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THE MALE CLIMACTERIUM*

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The word climacteric is derived from the Greek word climacter, which means "the round of a ladder." In its strictest medical usage, it may be applied to a particular period in the ordinary life span, during which the body is believed to undergo a radical change, such as puberty, the menopause or old age. Commonly it is employed to denote the changes associated with an abnormal menopause in women, and less frequently to describe similar disturbances in men during late middle life. The presence of such a condition in the male has been frequently challenged, often by high authority, because the ascribed symptoms and signs occur at a time when sexual libido, potency and spermatogenesis appear to be still undisturbed. However, the existence of the syndrome in the female is readily admitted by the same authors, despite the fact that the manifestations may make their appearance several years before, or even fifteen to twenty years after the cessation of ovulation and menstruation. By the same token, in the male all phases of testicular activity may not wax and wane simultaneously, either quantitatively or qualitatively.

The word climacterium, as commonly used and as employed here, represents an abnormal state of the body, initiated by a diminution in *certain* functions of the gonad and characterized by a variation from normal in the response of several glands of internal secretion. The term, therefore, is not used synonymously with the menopause in the female (merely a cessation of ovulation and menstruation), nor with loss of libido, potency and spermatogenesis in the male. It is used to denote a state of glandular maladjustment secondary to altered gonadal function. This maladjustment is clinically characterized by a wide variety of symptoms and signs, no one of which is pathognomonic, but which, when considered conjointly, constitute a diagnostically recognizable and therapeutically useful pattern.

In making a diagnosis of the male climacterium, several observers (1–10) have laid great stress upon the importance of quantitative determinations of urinary gonadotropins and 17-ketosteroids, emphasizing the fact that before the diagnosis

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should even be entertained, the excretion of gonadotropins should be high and that of 17-ketosteroids, low. Some investigators believe such a correlation to be of considerable value, but have been unable to find such an association in many of their patients (11–17). Still a third group of workers failed to make this correlation and doubt its value in the final classification of cases (18–29). The present study concerns 245 patients with the male climacterium which we have seen between January 1, 1938 and December 31, 1953—a period of sixteen years. These were culled from 577 patients in whom, on the basis of history and physical examination alone, the findings raised the question of this diagnosis.

METHOD OF STUDY

Subjects

The subjects of this study were selected from private practice, from the wards of Metropolitan Hospital, and from the outpatient departments of Flower and Fifth Avenue Hospitals and Metropolitan Hospital. Inclusion in the series depended upon whether or not the syndrome presented by the individual subject could meet the criteria of diagnosis.

Diagnostic criteria

In each subject, the diagnosis of the male climacterium was reached by (a) an analysis of symptoms; (b) the absence of physical signs pointing to organic disease; (c) the exclusion of other diseases such as low-grade, chronic infections, *e.g.*, brucellosis, lues or tuberculosis; (d) determination of urinary 17-ketosteroids; (e) bioassay of urinary gonadotropins, when possible; and (f) a therapeutic test alternating placebo and drug (Table 1).

In view of the debatable position of the male climacterium as a clinical entity, it seems necessary to make further comment on the manner in which these data were obtained.

(a) *Analysis of symptoms.* In taking the history, more than usual emphasis was placed upon allowing the patient to tell his own story uninterruptedly and uninfluenced by queries from the examiner. Upon conclusion of such a history, a single question was routinely repeated until the answer was an unqualified "No." This question was "Is there anything else you can add"? As soon as a

TABLE 1

Diagnosis of Male Climacterium

1. *History*
2. *Exclusion of other diseases*
   a. Infection
   b. Overwork; worry
   c. Mental states—melancholia
3. *Urinary hormone titers*
   a. 17-Ketosteroids
   b. Gonadotrophins
4. *Therapeutic test*

negative reply was received the interviewer changed to a pen or pencil of a different color, so that "volunteered" and "queried" replies might be later distinguished. At this point the interview might take one of two directions 1) an elaboration of the presenting history, or 2) a review of systems, and past personal and family histories. At all times, the use of leading questions was avoided, or if direct suggestions had to be made to enable the patient to understand the point on which information was sought, at least three alternatives were presented. For example, if weakness were offered as a presenting symptom, without qualification, and a simple request for modalities was not understood by the patient, it might be necessary to ask for the influence of specific factors, such as the time of day or night. In this instance, phrasing such as the following would be used. "Is your weakness worse in the morning, afternoon or evening, or is it influenced at all by the time of day or night?" In the final evaluation of these data, the part of the history volunteered or given in response to the question "Is there anything else . . .?" was always accorded highest rating. Unless all of the volunteered data were *compatible with* the syndrome, the diagnosis of male climacterium was discarded on the basis of history alone.

(b) *Absence of physical signs pointing to organic disease.* If an organic pathologic condition capable of producing the presenting manifestations was found on physical examination, the diagnosis of male climacterium was considered untenable. However, coexistence of organic disease and climacteric symptoms is not unknown. Most of the patients in the group, who were seen in private practice, represented a highly selected material, as they were usually interviewed because other physicians had already been unable to uncover an organic reason for their manifestations.

(c) *Exclusion of readily confusing diseases.* Chronic infections, such as brucellosis, lues and tuberculosis, were excluded insofar as possible by the use of specific laboratory tests for their detection. Metabolic diseases, such as diabetes mellitus (with which the symptoms of climacterium might be confused on superficial examination) were likewise eliminated by appropriate laboratory procedures. Overwork and overworry were ruled out as carefully as possible by attention to the pertinent portion of the history. Some purely functional disorders, such as melancholia and neurocirculatory asthenia could at times be eliminated on the basis of the history or physical examination, but at other times it was necessary to employ the therapeutic test.

(d) and (e) *Determination of urinary 17-ketosteroids and gonadotropins.* Because considerable emphasis has been placed upon the importance of the level of urinary gonadotropins and 17-ketosteroids in connection with the diagnosis of the male climacterium, determination of 17-ketosteroids was carried out in all of our subjects, and of gonadotropins in those for whom performance of the test could be arranged. The method used for assay of gonadotropins was that of Gorbman (30). The 17-ketosteroids were determined by the method of Gallagher, Koch and Dorfman (31) during 1938 and 1939, by the method of Talbot and his associates (32) during the period 1940 to 1943, and by the method of Drekter and his associates (33, 34) from 1944 to date.

(f) *Therapeutic test, alternating drug and placebo.* If the diagnosis remained in doubt after the results of all of the foregoing procedures were duly evaluated, then the patient was given the test of treatment.

In all patients, treatment was initiated by a series of three intramuscular injections weekly for two weeks. Testosterone propionate was the drug employed. During the first week, the individual dose was always 25 milligrams; this was continued through the second week, provided distinct relief had been obtained during the first week of therapy. If the effect was slight or equivocal, the dose was doubled during the second week of treatment. If there was some question of the effects of the injections being purely psychogenic, all medication was stopped at the end of the second week, and the patient was told not to have further treatment unless his symptoms returned. Upon the patient's return following such a recurrence he was told that treatment would be resumed. However, instead of receiving the steroid hormone, he was given a placebo, which consisted of the menstruum used for the solutions of testosterone propionate. If his response to this was good (disappearance of most or all of his symptoms), a psychic effect was considered proved and he was removed from the list of climacteric patients. If there was no improvement, he was asked to try treatment for a short time longer and, without his knowledge, drug was substituted for placebo. It should be emphasized here, that the response of the climacteric individual to the administration of testosterone is rapid and dramatic. If, under treatment with testosterone in the dosages and for the times mentioned, the patient was not significantly improved, it seemed apparent that the climacterium did not exist. If on the other hand, the injections of testosterone resulted in prompt dramatic relief not afforded by the placebo, it was equally clear that the diagnosis was correct. Although there are several conditions in which the nutrition and the general sense of well-being can be improved by the use of testosterone (for example, in the lowered cerebration, apathy and muscular weakness of senility), in our experience there is no condition in which the effects are more quickly noted than in the climacterium.

In many patients with climacteric symptoms drugs other than androgen are also indicated, such as vitamin mixtures, thyroid hormone, and autonomic nervous system depressants or stimulants. However, no such drugs were used in the present group of patients until a diagnosis had been established, for

TABLE 2

Cases Studied for Possible Presence of the Male Climacterium (16-Year Period)

Originally screened by history and physical examination		577
Excluded because of		
Infection	38	
Nutritional error	8	
Poor adjustment (*e.g.*, worry or overwork)	152	
Melancholia	13	
Results of therapeutic test	121	332
Male climacterium		245

testosterone alone will always improve the climacteric subject. Therefore its action should always be tested before there is an opportunity for confusion between its effects and those of some concurrently employed agent.

Among 577 patients who, on the basis of history and physical examination, might possibly have been suffering from the climacteric syndrome, the foregoing methods ruled out that diagnosis in 332 (Table 2). The remaining 245 were treated for the climacterium with the results to be described.

RESULTS

Further consideration of the male climacterium will be confined to observations made upon the 245 individuals, who fulfilled the criteria for diagnosis and responded promptly to therapy with testosterone but were unaffected by placebo.

Laboratory data

1. *The basal metabolic rate.* In the present study, by the term "normal basal metabolic rate" is meant one between minus 10 and plus 15 per cent of the normal for the age, sex and computed surface area of the individual. Figures above or below this level were noted as "high" and "low," respectively (Fig. 1). Of the climacteric subjects, 19.4 per cent had high rates and 17.2 per cent had low rates; in 63.4 per cent they were within the range of normal. In 83 apparently normal subjects of similar age and sex groupings, 5 per cent had a low basal metabolism, and none showed a high value (Fig. 1). In the individual patient, the basal metabolic rate was not of diagnostic value.

2. *Urinary 11-oxycorticoids.* The excretion of 11-oxycorticoids was above normal in 15.3 per cent of 26 climacteric individuals, and in 3.7 per cent of normally aging subjects in the same decades of life (Fig. 2). Appraisal of variations was based on the normal values given for the two methods employed in

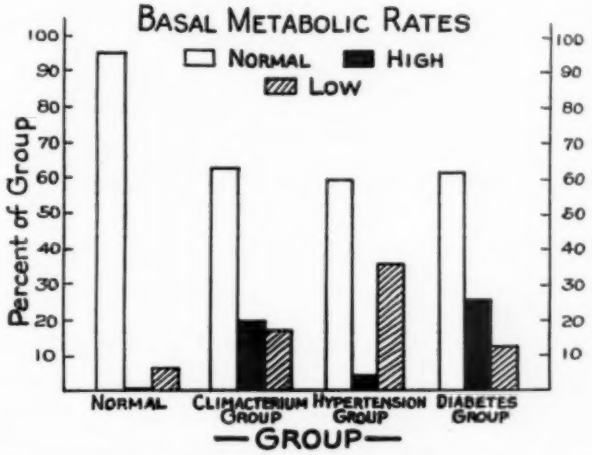

FIG. 1. The basal metabolic rate in 245 patients with the male climacterium compared with the rate in groups of normal, hypertensive and diabetic subjects. Basal metabolic rates between minus 10 and plus 15 per cent were considered normal.

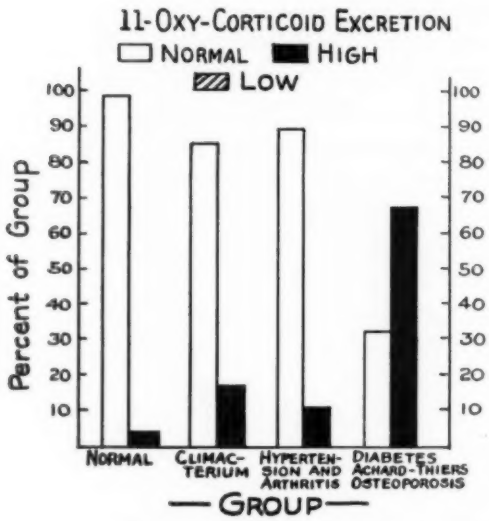

FIG. 2. The urinary "11-oxycorticoid" excretion of 26 patients suffering from the male climacterium, compared with the excretion in normal subjects and in those with "degenerative" diseases associated with aging. The normal range is that adopted by the original workers with the methods used (35, 36).

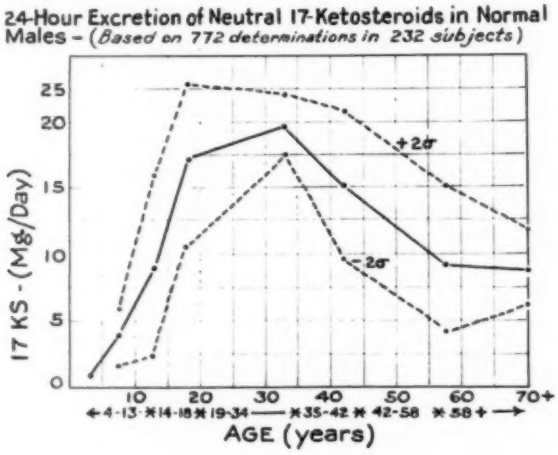

FIG. 3. Curve of urinary 17-ketosteroid excretion in males of various ages (*see* Ref. 37)

our determinations (35, 36). Although there was considerable fluctuation in individual values, the average rise above normal was not sufficiently marked to represent a significant difference.

3. *Urinary 17-ketosteroids.* Values for urinary 17-ketosteroid excretion were considered abnormal if they lay outside the range of values shown by the dotted lines (twice the standard deviation) in Figure 3 (37). On this basis, urinary 17-ketosteroids in 47.1 per cent of the 245 patients were within the normal range; in 19.2 per cent they were above, and in 33.7 per cent they were below these limits (Fig. 4). It would seem that in a significant number of climacteric

patients there is an alteration from the normal in the excretion of 17-ketosteroids; but in any given case, neither the degree nor the direction of the change, if any, can be predicted.

4. *Urinary gonadotropins.* Urinary gonadotropins were determined in 47 of the 245 patients (Fig. 5). A high average was observed only in the group between 55 and 60 years old. The scattering of values was so great that diagnostic significance could not be attached to a single determination in any given subject.

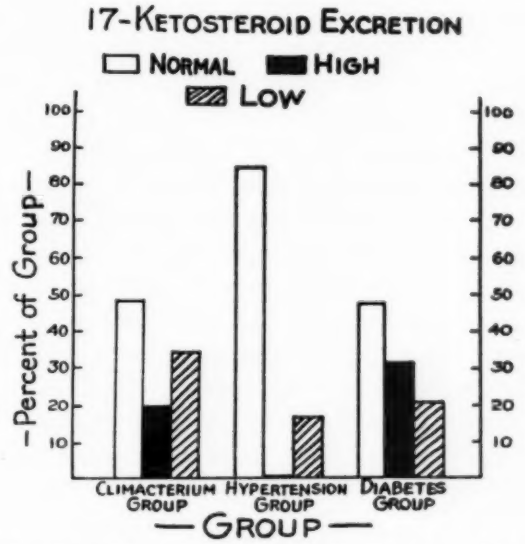

FIG. 4. Urinary 17-ketosteroid excretion in 245 climacteric males compared with that in hypertensive and diabetic patients. Values were considered normal if they fell within the range of twice the standard deviation, as shown in Figure 3.

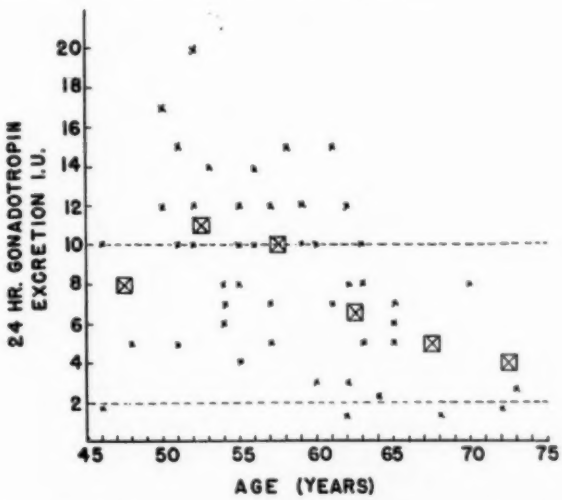

FIG. 5. Urinary excretion of gonadotropins in 47 climacteric males. Dotted lines demarcate the area of normal in relation to the method used (30). Box-enclosed crosses represent the arithmetic mean of all the values in the corresponding five-year period.

However, when all of the data were reviewed, there was a suggestion that the gonadotropins may vary in relation to the age of the patient and inversely as the duration of his symptoms, but show no correlation to the severity of his climacteric condition. These are only trends, and no conclusions can be drawn without statistical analysis of a very much larger series of cases.

5. *Correlation of values for urinary gonadotropins and 17-ketosteroids.* In Table 3 the titers for urinary gonadotropins and 17-ketosteroids are listed according to three age groups—45 to 54, 55 to 64, and 65 and above. The patients were also divided into those with normal, high and low values. In Table 4, a complete correlation of the urinary gonadotropins and 17-ketosteroids is attempted in the 47 subjects in whom both determinations were made. A combination of high gonadotropin and low 17-ketosteroid excretion was found in 9 of the 47 subjects (19.1 per cent). This is presumed by some workers to be the classic combination of hormonal findings without which a diagnosis of the climacterium should not be entertained (1–10). High gonadotropin and normal 17-ketosteroid excretions were seen in 6 subjects (12.8 per cent); normal or low gonadotropin and low 17-ketosteroid excretions in 23 subjects (49 per cent); and normal or low gonadotropin with normal 17-ketosteroid excretions in 9 of the individuals tested (19.1 per cent). Thus, approximately 32 per cent of the climacteric patients in this sub-group showed high urinary gonadotropins, and approximately 68 per cent showed low urinary 17-ketosteroids.

It is clear from a study of the laboratory data that no pathognomonic test exists for confirming the presence of the male climacterium.

TABLE 3

Results of Urinary Hormonal Assays in the Male Climacterium

Age of Subject (yrs.)	Gonadotropins (I.U./24 hrs.)				17-Ketosteroids (mg./24 hrs.)			
	No. of analyses	<2 I.U.	2 to 10* I.U.	>10 I.U.	No. of analyses	<8 mg.	8 to 12† mg.	>12.5 mg.
45–54	20	1	10	9	89	34	37	18
55–64	23	1	16	6	152	66	69	17
65 plus	4	2	2	0	4	3	1	0
Totals	*47*	*4*	*28*	*15*	*245*	*103*	*107*	*35*
Per cent		*8.1*	*59.9*	*32.0*		*41.5*	*43.1*	*15.4*

* Ninety per cent of normal values.

† Eighty per cent of normal values.

TABLE 4

Relationship of Urinary Gonadotropins to 17-Ketosteroids in the Male Climacterium

Gonadotropins	17-Ketosteroids	No. of Cases	Per Cent
High	Low	9	19.1
High	Normal	6	12.8
Normal or low	Low	23	49.0
Normal or low	Normal	9	19.1

Clinical manifestations

The clinical manifestations of the male climacterium may be general in nature, or affect predominantly some single anatomic system or functional unit of the body, such as the nervous, cardiovascular, gastro-intestinal or genito-urinary system. Some of the more commonly observed of these manifestations have been recorded in Table 5 with a notation of their frequency in the 245 patients of the study. More than 75 per cent of these patients complained of easy fatigability, difficulty in concentrating, failing memory, and restlessness with sleeplessness and heightened irritability or irascibility. Between 50 and 75 per cent were disturbed by palpitation and dyspnea unrelated to effort. Noted in 25 to 50 per cent of these subjects were loss of weight, weakness, muscular aches and pains, constipation, dizziness, anginal pain and a decrease in the force of the urinary stream. Still less frequently observed were hot flushes, sweating, intermittent claudication, coldness and numbness of the hands and feet, "dragging down" in the groins and spots before the eyes.

Most of these symptoms can be directly related to a lack of the known metabolic actions of testosterone, but few, if any, appear to be "sex-linked."

No one of these symptoms is pathognomonic. Indeed, all are rather common, and are seen in a wide variety of exhausting or degenerative diseases. However,

TABLE 5

Metabolic Effects of Testosterone, as Indicated by Change in Symptoms in 245 Climacteric Males

Manifestations	Total No.	No. Improved by Testosterone	Manifestations	Total No.	No. Improved by Testosterone
General			*Cardiovascular*		
Easy fatiguability	236	236	Palpitation, discomfort in region of heart, or "breathlessness"	167	160
Loss of weight	105	105	Vertigo, scotomata	81	78
Weakness	90	90	Anginal pain	62	49
Muscular aches and pains	89	75	Sweating	21	18
			Hot flushes	18	18
			Intermittent claudication	18	18
Nervous			*Gastrointestinal*		
Difficulty in concentration	219	189	Constipation	78	51
Loss of memory	200	180	"Bloating"	57	43
Restlessness, insomnia, irritability	195	175	*Urological*		
			Decreased force of urinary stream	80	80
			Dragging pain in groin	25	25

when fully characterized and weighted by means of the importance accorded them by the patient himself, they create in the mind of the observer a very definite picture which is not easily mistaken. In this connection, some analysis of the individual symptoms may be illuminating. Perhaps the most typical and most frequently related story is that of the business man who states that he tires easily, cannot concentrate on even the simplest of problems, is unable to remember even routine matters, is irascible to the point of being poorly tolerated by business associates or family, and finds sleep poor and unrefreshing. All these symptoms appear despite the fact that he is not overworking and has no reason to be worried about business or domestic affairs.

Further delineation of even the more common of these manifestations can be revealing as well as useful in differential diagnosis. The "spasmodic" nature of the manifestations of the female climacterium is not lacking in the male counterpart of this syndrome. Most of the symptoms are of this nature. For example, the easy fatigability and weakness may be present at any time of the day or night, and may appear suddenly without relation to added energy requirement. This is in contrast to the patient with hyperthyroidism, who starts the day full of energy but finds himself completely worn out after a period of activity, to a degree which is roughly inversely proportional to the severity of his thyrotoxic state. The weakness of Addison's disease or panhypopituitarism is constant in nature and represents a state of both mental and physical exhaustion. These same symptoms when noted in chronic infections vary in intensity with the severity of the infection. In the climacterium, capacity for muscular effort is little disturbed although muscular tone may be diminished, and the inclination to exert oneself lowered. The muscular weakness of the other conditions just mentioned is usually real. Again the fatigability of the climacteric patient differs from that of the subject with neurocirculatory asthenia, who always awakens tired, improves as late afternoon or evening approaches, and usually enjoys staying up half of the night.

The muscular aches and pains of the climacterium are fleeting and vary in appearance and intensity. A spasmodic quality is readily apparent.

The angina-like pain of the male climacterium (ref. 38—lit. cited) is usually not related to effort, is associated with deep sighing respirations ("breathlessness"), is not relieved by nitroglycerine, but is relieved promptly by testosterone.

The decreased force of the urinary stream associated with the male climacterium has often led to a mistaken diagnosis of prostatic hypertrophy. The sluggishness of the urinary flow in the latter condition is due to obstruction, whereas in the climacteric it is due to weakness of the bladder musculature. The same muscular metabolic fault accounts for the dull "dragging down" sensation often felt in the groin of patients who suffer from this syndrome. In other words, most of the symptoms of the male climacterium result from a loss of, or decrease in the anabolic activity of testosterone, and sexual function may be little, if at all disturbed.

Therapeutic data

In all instances, the climacteric patients in this series received at first only testosterone propionate by intramuscular injection in sesame oil[1]. All of them were improved in greater or lesser degree by the use of such material. Dosages ranged from 25 to 100 milligrams three times weekly; 155 of the 245 patients were satisfactorily relieved by the smallest of these doses, whereas an additional 53 required the supplemental use of other hormones to obtain complete relief (Table 6). Once complete relief was established and maintained for as long as three weeks, dosages were decreased and, if there was no return of symptoms, completely discontinued. Beyond the trial period of two weeks, an effort was made in most cases to continue therapy orally, by intraoral absorption, or with a combination of tablets intraorally and the pellets subcutaneously. The daily intraoral absorption of 20 milligrams of testosterone propionate tablets was

TABLE 6

Therapy in 245 Patients with Manifestations of the Male Climacterium

Treatment	No. of Patients
Androgen only	192
Androgen plus estrogen	15
Androgen plus thyroid	35
Androgen plus estrogen plus thyroid	3
	245

usually the equivalent of 25 milligrams of testosterone propionate intramuscularly three times weekly. If a larger dose was needed, it was always necessary to use a supplement of pellets implanted subcutaneously. Each 75-milligram pellet yielded approximately 0.5 milligram of material daily. Milligram for milligram the weekly amount thus absorbed was about three times as effective as the weekly dose by injection. Thus, six pellets implanted subcutaneously produced about the same effect as an injection of 25 milligrams of testosterone propionate in oil three times weekly. "Wearing off" of the effect was noted in conjunction with the continuous use of testosterone, and was best avoided by intermittent rather than steady administration. For this reason, pellet implantations should never be used exclusively. It is best to give only a portion of the necessary dose in this fashion. In addition to this basic dose, intraoral or intramuscular testosterone ensures a sufficiently irregular absorption to afford the rhythmic variations apparently essential to the optimal physiologic effect. When necessary to use subcutaneous implantation, about two thirds of the necessary dose was given by this route and the remaining one third as a daily intraorally

[1] All placebos and testosterone preparations used in these studies were furnished through the courtesy of Dr. Edward Henderson of Schering Corporation, Bloomfield, N. J.

absorbed tablet. With the newer "depot" testosterone, it may be possible to avoid pellet implantation entirely in climacteric cases, and to space injections at intervals of two to three weeks.

Androgenic plus estrogenic therapy was required in 18 of the 245 patients (Table 6). For the most part these compounds were administered separately, although some successful mixtures are available. If these drugs are given by the intramuscular route, the ratio of the weekly dose in milligrams of testosterone propionate in relation to estradiol benzoate or dipropionate, should be approximately 75 to 1.

The equivalent of this ratio can be maintained equally well by some other estrogen administered by the same or a different route. As a rule we gave the estrogen by mouth and preferred ethinyl estradiol. It was necessary to add estrogen to the regimen in those cases in which the predominant symptoms were closely related to activity of the autonomic nervous system. These included flushes, sweating, palpitation and vertigo.

Evidence of a disturbance in thyroid function was present in 38 of the 245 subjects treated for the male climacterium, and complete restitution of health was not accomplished until small doses of desiccated thyroid (rarely exceeding 1 grain daily) were added to the regimen. In most instances in which thyroid hormone was employed, the patients were overweight, sluggish, and subject to repeated minor infections such as sore throats, nasal colds and skin infections.

The comment is often made that testosterone should not be employed under any circumstances in older men, as its sex-linked action will increase sexual activity to a detrimental point—for instance in those who suffer from coronary sclerosis. In the present series of cases, there seemed to be little tendency toward increased sexual activity with doses of the steroid which afforded satisfactory metabolic responses (Table 7). From this table it will be noted that in the earlier age group (42 to 60 years), of 77 individuals who complained of a "general loss of vigor", 73 were improved; whereas of 43 in the same group who had noted loss of potentia only 13 regained such activity. In the older age group (60 to 84 years) the differences were even more striking; muscular and mental vigors were improved in 50 of 52 subjects, whereas lost potentia was partially or completely restored in only 2 of 45 patients.

It should be emphasized that in the treatment of the climacterium the dosage of hormone is best decreased as soon as all symptoms have been fully controlled for from one to three weeks. In the present series, if there was no return of

TABLE 7

Influence of Testosterone on Climacteric Complaints at Different Age Levels

Age group (years)	42–59	60–84
Number in each group	111	65
Improved vigor	73 [77]*	50 [52]*
Increased potentia	13 [43]	2 [45]

* Numbers in brackets indicate the number of patients who had lost the corresponding attribute prior to treatment.

TABLE 8

Follow-up Five Years or More in 109 of 180 Cases of the Male Climacterium*

Total Period of Hormonal Treatment Required	Treatment Intermittent	Treatment Continuous	Totals
1 mo. or less	0	8	8
Over 1 mo. to 3 mos.	2	15	17
Over 3 mo. to 6 mos.	41	4	45
Over 6 mo. to 1 yr.	20	1	21
More than 1 yr.	17	1	18
Total No. followed for 5 yrs. or more	*80*	*29*	*109*

* Sixty-five of the 245 patients were first observed within the last five years before the series was closed, and are therefore not included.

symptoms while decreasing the dose of hormone, therapy was eventually stopped, and renewed only upon a return of symptoms. An attempt was made to follow our patients for at least five years after initiation of treatment. In Table 8 is shown the approximate duration of therapy in each of the 109 patients in whom it was possible to complete such a five-year review. Of these subjects, 80 were treated intermittently and 29 continuously. Forty-five or 41.3 per cent required a total of three to six months of treatment, but this was continuous in only 4 of the cases. Thirty-nine subjects were treated for more than six months, but in only 2 of these was continuous therapy required to keep them symptom-free. Continuous therapy for long periods of time is not recommended and can do actual harm, as in 1 of the 2 patients just mentioned. Without consulting his physician, this man continued the use of testosterone for a little over eight years in the equivalent of daily doses of testosterone propionate in oil ranging from 50 to 150 milligrams. He stated that he used the dose he found necessary to keep him symptom-free. At the end of this period he had a low titer of urinary gonadotropins, and complete suppression of spermatogenesis, as shown by semen examination and testicular biopsy. Fortunately, one and a half years following the cessation of therapy, the semen was again entirely normal. From Table 8 it is clear that such prolonged periods of treatment are rarely necessary, as only one sixth of our patients required treatment beyond the first year of observation.

DISCUSSION

1. *The existence of the male climacterium.* Evidence for and against the existence of the male climacterium has been accumulating ever since the development of potent synthetic androgenic materials. Any attempt to reason by analogy from the female is fraught with considerable difficulty, as organ regulation and primary sexual activity seem to be somewhat differently directed in the two sexes, at and beyond "middle life." Engle (39) has recently made a serious attempt to distinguish these activities on developmental and anatomic grounds. The subject was reviewed by Witschi (40) several years ago. In neither of these presentations was it possible to fix with certainty the specific functions of the different types of cells in either gonad. Furthermore, the discussion of both

these papers emphasized our lack of knowledge of the role played by the several hormones in regulating the activity of the cellular elements of both the ovary and the testis. There is as yet little firm ground on which to base an anatomic hypothesis which will explain the relative frequency of the climacterium in the female and its somewhat rare occurrence in the male.

In an effort to place the diagnosis of the male climacterium on a firm basis several investigators have considered a low level of urinary 17-ketosteroids and a high level of urinary gonadotropins essential to the diagnosis (1 to 10). Such variation in these urinary excretion products is not uncommon, though by no means always present in individuals suffering from the female climacterium (11 to 29). In the female, it would appear that the titers bear some relationship to the *duration* of the climacteric state, but little or no relation to its *severity* or *response to treatment* (25). In the regulation of hormonal activity, widely different roles have been ascribed to the male and female gametogenic cells of the gonad ((38, 39); *see also* discussion). It is not surprising that at the change of life, alterations in the excretion of hormonal products are dissimilar. In fact, today there is probably more evidence for (18 to 29) than against (1 to 10) a more or less complete dissociation between the gonadotropic and 17-ketosteroid excretion in the male with climacteric symptoms.

The lack of methods by which a diagnosis of the climacterium can be made objectively has resulted in a denial of its existence by some workers. However, those who have followed many patients clinically will be loathe to assume such an extreme position.

Three things seem to lead to a definite diagnosis of the male climacterium: 1) the nature of the historical data in a large number of individuals, 2) the exclusion of other diseases, and 3) the response to therapy. There is no pathognomonic symptom or sign of the climacterium, either male or female. However, when a combination of symptoms and signs is suggestive of the syndrome, and no other cause can be found, this should be substantial evidence for its existence. In such cases, the therapeutic test affords further confirmation. Only agonadism and hypogonadism respond as promptly and dramatically to the exhibition of androgen. There is relief following a single injection of an adequate amount of hormone. Those who would doubt the value of this test emphasize the point that even normal people will exhibit anabolic activity following the use of an androgen. This is quite true; but there are differences. For example, the response in the nonclimacteric subject is never as prompt. For several years we have used testosterone in thin, asthenic but otherwise normal males to increase their weight and often their strength. Such patients require several weeks to show any measurable improvement with androgen therapy. When the climacterium exists, the change to a sense of well being is prompt and dramatic. We have also employed androgens to improve the status of senile individuals. As a general rule, subjects of both sexes can be helped by such therapy. However, there are rarely any obvious clinical changes prior to ten or fourteen days of treatment. We have yet to see any *subjective* response to androgen which is as rapid as that made by the climacteric individual. In our opinion, the trial of grouped clinical findings,

the absence of other detectable disease and the promptness of therapeutic response fully justify the use of the male climacterium as a diagnostic entity. After all, the major objective of diagnosis is to point the way to effective therapy. Whether the male climacterium is a correct or incorrect term for the syndrome is of secondary importance. Of primary interest is the fact that androgenic therapy relieves the suffering of these individuals and medication with placebo does not.

Further elucidation of this problem of the male climacterium holds more than academic interest for the clinician. However, until such time as its existence can be afforded general and unequivocal confirmation, it seems desirable to relieve human suffering if and when we can. This can be accomplished with testosterone under the conditions fulfilled in this study. The danger of prescribing treatment in the absence of pathognomonic findings, either clinical or laboratory, lies in the abuse and overuse of the effective therapeutic agent. Such overuse is not necessary in cases of the male climacterium as defined here. A two-week trial of therapy as outlined will bring major relief to any sufferer from the climacteric syndrome. It will have little effect in the dosages mentioned in any other condition, with the possible exception of a readily recognizable lesion in the testis associated with, or resulting in hypogonadism or agonadism.

SUMMARY AND CONCLUSIONS

1. The term climacteric is defined in accordance with its usage in the present study. By no single pathognomonic symptom, sign or laboratory finding is the diagnosis established. The diagnosis rests upon (a) the exclusion of other diseases, (b) the history, (c) normal findings on physical examination (rarely, unrelated disease may be present), (d) altered titers for urinary gonadotropins and 17-ketosteroids, and (e) a positive result with the therapeutic test.

2. Among 577 men in whom the condition was suspected as a result of history and physical examination, its presence was presumptively established in 245.

3. No characteristic change was observed in the basal metabolic rate.

4. Urinary "11-oxycorticoid" excretion was above normal in 15.3 per cent of the 26 individuals in whom the determination was made.

5. Urinary 17-ketosteroid values were below normal for age in 33.7 per cent of the 245 patients.

6. Urinary gonadotropins, assayed in 47 instances, varied markedly from subject to subject, but showed a tendency to be high between the ages of 50 and 60 years. In these 47 individuals a combination of high gonadotropin and low 17-ketosteroid output was observed in 9, or 19.1 per cent.

7. Clinical manifestations in these 245 men are detailed; the most common were easy fatigability, difficulty in concentration, failing memory, restlessness, sleeplessness, and heightened irritability. Other less frequently observed symptoms are described and their incidence recorded. The "spasmodic" nature and other peculiar modalities of these manifestations of the male climacterium are delineated.

8. A therapeutic regimen is described, which in selected instances may include not only androgens, but also estrogens and thyroid hormone.

9. Many men (and their families) can be saved from long periods of discomfort by the judicious use of androgens. There is no need to abuse such therapy. The rapid complete response of the climacteric male to appropriate treatment obviates the necessity for the prolonged and ill advised use of androgens in men suspected of having this condition.

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LOW-DOSAGE ANDROGEN-ESTROGEN THERAPY IN THE OLDER AGE GROUP*

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The climacteric in both men and women designates that period in life when the gonads fail to respond to stimulation by pituary gonadotropin. With gonadal failure, the secretion of androgen or estrogen decreases and brings with it the well-known signs of deficiency.

A relative increase in secretion of the heterogenous hormone accompanies the general decrease in output of sex hormones. Thus, in women relative androgen output rises, as manifested by mild hirsutism and slight enlargement of the clitoris; there may also be enhanced libido and falling of hair from the head. The relatively increased estrogen secretion in men may result in diminished libido, loss of body hair, and occasionally in cracking of the voice.

Once the climacteric becomes established and the pituitary ceases to be overactive, the testes and ovaries show little activity. Less gonadotropin is secreted, so the gonadal stimulus becomes minimal. The deficient elaboration of androgen and estrogen results in gradual drying up or atrophy of the tissues supplied by the gonadal hormones. Loss in tone of the skin in both sexes, and flabbiness of the breasts, atrophic vaginitis with loss of vaginal rugae, and an irritating discharge in women, are familiar accompaniments of these alterations.

Whereas frank symptoms of estrogen deficiency occur in some women as the menses cease, others show few objective signs. The physician sees many women in the postmenopausal period who complain of fatigue, depression, arthralgia, headaches, insomnia, forgetfulness, and loss of libido—subtle indications of changes in mind and body accompanying the alteration in endocrine secretion. These women often feel insecure and inadequate. Men are affected similarly by a diminution in the endocrine function of the testes. Those in older age groups often show subjective symptoms that resemble those in postmenopausal women. They become nervous and irritable and complain of loss of memory for familiar things, slow responses, diminished libido, headache, and vague pains.

All of these disturbances indicate that the patients would benefit from moderate sex hormone replacement therapy, and alleviation of symptoms has been accomplished by the administration of androgen and estrogen in the respective sexes. These good results can be enhanced by administering the sex hormones in combination. Thus their anabolic and tonic effects re-enforce each other, and

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some disadvantages inherent in therapy with a single hormone are overcome. For example, withdrawal bleeding, worrisome after cessation of the menses, is unlikely to occur. The occasional fullness of the breasts noted as a sequel to estrogen therapy is avoided.

Full sex hormone replacement does not appear to be necessary in menopausal or postmenopausal women or in men in the older age groups. Furthermore, as the tonic and anabolic effects are enhanced, androgen and estrogen in combination evoke an excellent therapeutic response, even when given in very small doses.

PRESENT STUDY

A low-dosage androgen-estrogen combination in tablet form was tested in 61 menopausal or postmenopausal women and 9 men (all physicians) in the older age groups. Each tablet contained 1 mg. of methyltestosterone and 0.001 mg. of ethinyl estradiol.[1] The low doses of the hormones seemed sufficient in these older men and women (most of whom were postmenopausal) to furnish a general tonic effect and to replace hormone deficiencies, yet small enough to avoid adverse effects, such as postmenopausal bleeding.

Three-fourths, or 46 of the 61 women were between the ages of 50 and 68 years, 14 were aged 40 to 49 years, and 1 was 39 years of age. The 9 men ranged in age from 57 to 67 years.

These 70 patients were not acutely ill. Their complaints, as shown in Table 1 for the women and Table 2 for the men, seemed to them to be mainly changes in personality. They were tired, nervous, and disturbed by petty irritations that previously made no impression on them. The women were variously subject to hot flashes, depression, headache and arthralgia. Some of them had vaginitis and the irritating vaginal discharge that accompanies menopausal disappearance of vaginal rugae. Their husbands complained of burning in the urethra following coitus which, in general, was unsatisfactory to both. Most of the women had a castrate type of vaginal smear. Among the complaints of the men were asthenia, diminished libido, depression, arthralgia and headache. Some cried easily and were perplexed by a loss of memory for familiar things.

The average daily dosage was two tablets for both male and female patients, or a total of 2 mg. of methyltestosterone and 0.002 mg. of ethinyl estradiol. One man received one tablet every other day. Five women are still under therapy. The time of treatment in the other patients varied from three months to two and a half years. Forty-three of the 70 patients received the low-dosage hormone combination for from nine to eighteen months.

RESULTS

We were gratified to note in this series of patients the predominantly good response that followed the administration of the small doses of methyltestosterone and ethinyl estradiol in combination. A general tonic effect became apparent. Dispositions usually improved and the patients had a better mental outlook.

[1] Supplied as Ortinyl by the Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

TABLE 1

Results of Low-Dosage Androgen-Estrogen Therapy in Menopausal and Postmenopausal Women

Patient		Symptoms	Therapy		Vaginal Smear*		Result	Comment	Blood Pressure (mm. Hg)	
Name	Age		Dose (tablets per day)	Duration (months)	Before	After			Before	After
A. Birnberg's Series										
R. E.	55	Depressed	2	16	Castrate	2+	Excellent		140/90	110/60
B. F.	42	Flushes, decreased libido	2	18	Castrate	2+	Excellent	Improved libido	150/96	116/70
M. C.	46	Flushes, premenstrual tension	2	11	Castrate	3+	Good	Improved libido	160/94	120/70
F. C.	52	Vaginal itch, poor coitus	2	9	Castrate	2+	Fair	Improved libido	130/90	130/90
N. A.	49	Tired, irritable	2	18	Castrate	2+	Excellent	Improved libido	160/120	142/90
H. B.	51	Tired, irritable	2	8	2+	Same	Excellent	Improved libido	180/100	120/70
B. B.	42	Tired, flushes, irritable	2	11	3+	Same	Fair		160/90	118/68
C. W.	55	Painful joints, flushes, tired, decreased libido	2	11	Castrate	2+	Excellent	Improved libido	160/90	130/80
E. W.	56	Flushes, painful joints	2	19	Castrate	2+	Excellent		156/90	138/70
F. W.	46	Nervous, flushes, tired	2	26	Castrate	Same	Excellent		160/100	126/80
A. D.	42	Irritable, crying	2	11	4+	Same	Excellent	Improved libido	150/100	110/60
C. K.	59	Tired, irritable	2	11	Castrate	2+	Excellent	Improved libido	156/106	134/80
L. P.	56	Irritable, painful joints	2	10	Castrate	2+	Good		140/90	140/80
I. L.	58	Tired, irritable, painful joints	2	10	Castrate	2+	Excellent		160/94	138/80
I. K.	60	Tired, irritable, vaginal discharge	2	10	Castrate	2+	Good		130/80	130/80
L. M.	55	Headaches, tired, forgetful	2	11	Castrate	2+	Excellent		180/100	146/80
F. R.	54	Headaches, irritable	2	8	3+	Same	Poor		146/70	130/60

F. R.	54	Headaches, irritable	2	8	3+	Same	Poor			

TABLE—I (*Continued*)

M. S.	56	Tired, forgetful, irritable	2	14	Castrate	2+	Excellent	Improved libido	160/94	130/80
I. V.	56	Headaches, forgetful	2	12	Castrate	2+	Excellent		150/100	132/80
L. T.	59	Tired, irritable, painful joints	2	16	Castrate	2+	Good		150/92	126/70
R. V.	52	Tired, irritable, forgetful	2	15	Castrate	2+	Excellent	Improved libido	162/96	139/80
L. K.	49	Forgetful, flushes, tired	2	12	3+	Same	Poor		140/80	140/80
V. F.	52	Tired, forgetful, irritable	2	12	Castrate	2+	Excellent	Improved libido	150/90	120/70
A. D.	64	Depressed, crying, tired	2	12	Castrate	2+	Excellent		154/100	120/70
P. C.	48	Backache, tired	2	6	Castrate	2+	Excellent		156/88	124/70
F. L.	59	Burning in vagina, tired	2	11	Castrate	3+	Vaginitis improved	Outlook better, less tired	180/102	190/100
M. C.	40	Lower back pains	2	6	3+	Same	Feels well		140/80	110/70
M. L.	46	Flushes and sweats, tired	2	18	Castrate	2+	Excellent		160/100	116/70
H. L.	39	Flushes, tired	2	15	Castrate	2+	Excellent	Improved libido	150/90	120/70
D. M.	51	Flushes, painful joints, tired	2	13	Castrate	2+	Excellent	Improved libido	166/102	130/100
F. O.	55	Tired, salty taste in mouth	2	5	3+	Same	No result		120/70	120/70
E. R.	51	Flushes, tired, arthritis	2	12	Castrate	2+	Excellent	Improved libido	170/100	120/70
P. R.	54	Flushes, pains in joints	2	24	Castrate	2+	Excellent		166/80	130/70
B. R.	57	Vaginitis, tired	2	19	Castrate	2+	Excellent		150/90	120/70
B. S.	53	Backache, tired, painful coitus	2	7	Castrate	2+	Good	Improved libido	158/90	130/70
J. S.	57	Backache, tired	2	30	Castrate	2+	Good		148/96	116/70
F. S.	60	Flushes, backache	2	17	Castrate	2+	Excellent		170/110	140/90
C. S.	56	Vaginal itching	2	17	Castrate	Same	Excellent	Patient bled when taking 1.25 mg. Premarin daily	140/110	120/90
F. S.	42	Painful coitus, backache	2	10	4+	Same	Excellent		144/90	120/66

TABLE—1 (*Continued*)

Patient		Symptoms	Therapy		Vaginal Smear*		Result	Comment	Blood Pressure (mm. Hg)	
Name	Age		Dose (tablets per day)	Duration (months)	Before	After			Before	After
B. Kurzrok's Series										
B. C.	46	Asthenia, flushes	1	10	Normal	3+	Good		168/110	146/98
J. G.	62	Asthenia, nervous	1	3	Castrate	1+	Good		176/120	162/100
A. A.	57	Asthenia	1	7	Castrate	2+	Good		148/90	126/82
P. F.	62	Asthenia	1	12	Castrate	1+	Good		160/80	120/80
F. D.	58	Jittery	1	5	Castrate	1+	Good		172/110	144/100
H. S.	51	Quarrelsome	1	13	Castrate	2+	Good	Personality change	184/126	142/92
B. S.	60	Flushes, asthenia	1	Under therapy	Castrate	2+	Good		138/92	136/90
B. D.	49	Depressed	2	9	Poor estrogenic function	1+	Dubious	Probable depressed psychosis	130/90	130/90
M. S.	64	Asthenia	1	5	Castrate	1+	Excellent		172/90	138/82
M. B.	68	Flushes, tired	1	6	Castrate	2+	Good		162/96	138/80
J. J.	57	Nervous, quarrelsome	1	Under therapy	Castrate	1+	Good	Flushes developed, which soon stopped	184/110	160/96
M. D.	54	Asthenia	1	4	Castrate	1+	Poor	Did well on Cortate tablets	90/70	102/70
W. F.	50	No energy	1	7	Poor estrogenic function	1+	Good		156/108	130/86
T. R.	49	Flushes, asthenia	1	5	Normal	3+	Good		176/90	140/92
S. G.	54	Asthenia	1	8	Castrate	2+	Good	Added thyroid gr. 1 daily	162/92	136/88

TABLE—1 (*Concluded*)

B. B.	57	Asthenia, nervous	1	11	Castrate	2+	Good		158/88	122/80
M. D.	57	Dizzy, asthenia	1	Under therapy	Castrate	Castrate	Good		176/104	152/100
F. G.	50	Flushes, jittery	1	8	Poor estrogenic function	1+	Good		166/102	144/98
B. J.	60	Depression	2	12	Castrate	2+	Moderate		170/92	142/88
F. S.	52	Anxiety, depression	2	Under therapy	Castrate	2+	Good		148/84	122/80
J. H.	57	Weakness, depression	2	Under therapy	Castrate	1+	Good		160/92	138/84
C. K.	61	Tired in P.M.	1	4	Castrate	2+	Good		154/90	132/88

* All smears were carefully checked for malignancy before onset of therapy and rechecked one year later. No interval smears.

TABLE 2

Results of Low-Dosage Androgen-Estrogen Therapy in Men in Older Age Groups

Patient		Symptoms	Therapy		Result	Comment	Blood Pressure (mm. Hg)	
Name	Age		Dose (tablets per day)	Duration (months)			Before	After
Birnberg's Series								
P. W.	62	Forgetful, irritable, contrary, slow responses	2	16	Excellent	Improved libido	180/160	130/90
I. L.	67	Irritable, headaches, quarrelsome	2 for 4 mos.; then 1	11	Excellent	No change in libido	150/90	136/70
B. K.	65	Forgetful, cries easily, headaches, painful knees	2	11	Excellent	Improved libido	160/100	140/75
S. C.	66	Headaches, painful back, irritable	2; more if necessary	12	Poor	No change	150/100	136/80
B. K.	66	Headaches, irritable, forgetful	2	12	Excellent	Improved libido	180/130	142/90
H. W.	59	Headaches, irritable, failure to remember	1 every other day	16	Excellent	No change	148/90	120/70
L. S.	57	Headaches, irritable, cries easily, forgetful, pains in joints	2; could not reduce dosage	13	Excellent	Improved libido	160/110	130/70
S. C.	60	Irritable, forgetful, slow responses	2	14	Excellent	Improved libido	190/120	130/80
M. K.	59	Irritable, headaches, pains in joints	2	16	Excellent	Improved libido	230/160	146/90

They grew alert and responsive. Side effects, including uterine bleeding, were notably absent. Bleeding was avoided with this androgen-estrogen combination in a 56-year-old woman in whom it had occurred following the administration of conjugated estrogens in a dosage of 1.25 mg. daily.

Among the women, symptoms including fatigue, irritability, flushes, nervousness, headache and vague pains disappeared in 27 (44 per cent). A good result with partial alleviation of symptoms was obtained in 24 (39 per cent) and a fair degree of improvement in 5 (8 per cent). The results are shown in Tables 1A and 1B.

A favorable personality change occurred in 1 patient who formerly was very quarrelsome.

Fifteen of the women with an excellent or good response reported that they were aware of increased libido.

The character of the vaginal mucosa changed under treatment, and there was relief of vaginitis. Vaginal rugae, almost completely absent before therapy, developed slightly.

During therapy the vaginal smear changed from a castrate type to a 2+ or 3+ degree of cornification in 38 (62.3 per cent) of the women.

Four women responded poorly to this treatment. One patient in whom improvement was dubious may have had a depressive psychosis.

As shown in Table 2, 8 of the 9 men were relieved of their complaints.

Irritability and headaches disappeared, ability to remember familiar things returned, and the patients lost their former sense of frustration. These men were able to pursue their usual activities with energy and enjoyment.

Six men reported improvement in libido, whereas 2 who had a good response noted no change in this respect.

In 1 male patient, the benefits could be maintained with one tablet daily after an initial four months of therapy with a higher dosage.

Increasing the dosage above two tablets per day failed to better the status of the 1 patient who had shown little improvement.

Effect on Blood Pressure

Incidental to the general study of the low-dosage methyltestosterone-ethinyl estradiol combination in men and women of older age groups, there was an unexpected result which became apparent with sufficient consistency to warrant comment. There had been no primary intention to study the effect upon blood pressure of the hormones combined in the present ratio. It was interesting, therefore, to note that in a majority of these 70 patients, blood pressure was reduced from pretreatment levels. This observation appears significant in view of the fact that the blood pressures of some of the patients before treatment were elevated to hypertensive levels and no other drug was administered during the period of combined hormone therapy. None of the patients received any hypotensive, antihypertensive, or sedative drugs.

All 9 men showed a lowering of blood pressure (Table 3). The individual reductions are recorded in Table 2. Some of the reductions were striking, as in the

TABLE 3

Effect on Blood Pressure: Men

Age		Blood Pressure Before Treatment	Blood Pressure After Treatment
	59	230/160	146/90
	62	180/160	130/90
	66	180/130	142/90
	57	160/100	130/70
	60	190/120	130/80
	59	148/90	120/70
	65	160/100	140/75
	66	150/100	136/80
	67	150/90	136/70
Average	62	172/117	134/79

case of 62-year-old patient, P. W., who had a pretreatment blood pressure of 180/160 which fell to 130/90 after sixteen months of therapy. Patient M. K., aged 59 years, had a blood pressure of 230/160 before therapy; after treatment it was 146/90.

Among the 61 women, the blood pressure in 11 before treatment was within normal limits and no essential change occurred. In the remaining 50 women the pretreatment blood pressure was elevated to some degree, the diastolic pressure in each being 90 or above. Treatment with the androgen-estrogen combination brought about no essential change in 11. In the other 39 of this group, including some with blood pressures in the hypertensive range, the pressure was reduced in every instance (Tables 4 and 5).

Summarizing the responses in both men and women, a reduction in blood pressure occurred following treatment in 48, or 81 per cent, of the 59 patients with initial high pressure readings.

These observations on the hypotensive effect of minute amounts of methyltestosterone combined with ethinyl estradiol concur with those on the reduction of blood pressure achieved by Borgström (1) with low-dosage androgen-estrogen combinations in long-standing cases of essential hypertension refractory to ordinary conservative treatment. A tablet preparation he used for maintenance therapy contained 4 mg. of methyltestosterone and 0.004 mg. of ethinyl estradiol, so that the hormones were present in the same ratio as in our combination.

TABLE 4

Effect on Blood Pressure: Women

Blood Pressure Before Treatment	No. Pts.	Results of Treatment	
		Blood pressure reduced	No essential change
Normal	11		11(100%)
Elevated—diastolic pressure 90 or above	50	39(78%)	11(22%)

TABLE 5

Effect on Blood Pressure: Women (12 Selected Patients)

Age		Blood Pressure Before Treatment	Blood Pressure After Treatment
	51	180/100	120/70
	51	184/126	142/92
	55	180/100	146/80
	60	170/110	140/90
	49	160/120	142/90
	50	156/108	130/86
	59	156/106	134/80
	56	140/110	120/90
	57	184/110	160/96
	58	172/110	144/100
	62	176/120	162/100
	46	168/110	146/98
Average	55	169/111	141/89

Ekehorn (2) reported his own case of severe hypertension treated by Borgström's method. His extremely high blood pressure could be lowered and maintained near normal levels by the use of an androgen-estrogen regimen combined with Papaverine and calcium. He used a buccal tablet containing methylestosterone and ethinyl estradiol in the same ratio as in our tablet.

The degree and consistent occurrence of reduction of blood pressure observed in our patients, and the substantiation of this effect furnished by the work of the Swedish investigators, would indicate that the hypotensive effect of the combined hormones was not a mere coincidence. It appears that further investigation is warranted.

SUMMARY

An androgen-estrogen combination containing 1 mg. of methyltestosterone plus 0.001 mg. of ethinyl estradiol per tablet was administered for varying periods to 61 menopausal or postmenopausal women and 9 men. Presenting symptoms were alleviated in 8 of the 9 men. Good or excellent response was obtained in 51 of the women, and a fair degree of improvement in 5 others. In addition to exerting a general tonic effect, this therapy brought about favorable personality changes. The patients lost their former irritability, nervousness, and sense of fatigue. Most of the men and 15 of the women reported increased libido. Side effects were notably absent.

Of interest was the hypotensive effect of this low dosage androgen-estrogen combination. In all of the men, and in 78 per cent of the women initially high blood pressures were reduced after extended treatment with this combination of hormones alone. In all but a few instances, diastolic pressures above 90 were lowered to 90 or below. The confirmatory evidence cited makes this finding appear to be more than a coincidence.

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PREPARATION OF THE GERIATRIC PATIENT UNDERGOING SURGERY OF THE BILIARY TRACT*

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During the past fifty years there has been a progressive increase in the proportion of our population in the older age group. In 1951, there were 4,017,000 persons 75 years of age and over in the United States. This amounted to 2.6 per cent of the total population (1). The greater incidence of biliary-tract disease in this age group is well known. For these reasons surgeons are encountering the problems in management of geriatrics patients with biliary-tract disease with increasing frequency. Many of these problems are complicated. Acute cholecystitis, choledocholithiasis and carcinoma of the biliary tract may be considered as complications of gallstones that occur much more frequently in the aged. The surgical treatment of these conditions is attended by relatively high morbidity and mortality.

In the United States in 1951 there were 5,724 deaths from cholelithiasis and cholecystitis, representing a death rate of 3.7 per 100,000 population. Among those aged 75 and over there were 1,682 deaths from these two causes. This is equivalent to a death rate of 41.9 per 100,000 population and represents 29.4 per cent of the total deaths from these causes (1). In a recent analysis of mortality following biliary-tract surgery, Glenn and Hays (2) found that over the past twenty years infection has become better controlled, whereas degenerative disease processes have become a more important factor.

It is apparent that only by the most careful evaluation and preparation, by the performance of the simplest and most direct operative procedure, and by the most conscientious postoperative management can biliary-tract surgery be made safer. Patients with acute surgical illnesses are remarkably vulnerable when any additional demand is made on their limited reserves.

CLINICAL MATERIAL

During the 21-year period from September 1, 1932 to September 1, 1953, fifty patients aged 74 years and over were treated surgically for non-malignant disease of the biliary tract on the pavilion services of The New York Hospital-Cornell Medical Center. In 4 patients of this group, additional procedures were performed three months to six years following the initial cholecystostomies. In the ten years from 1933 through 1942 there were 9 operations, with a mortality rate of 22.2 per cent. There were 45 operations performed between 1943 and

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1953, with a mortality rate of 8.9 per cent. During the latter period, patients accepted for surgical treatment were older than those in the preceding period.

Fifty-four operations were performed in 50 patients: 24 (44.4 per cent) were for acute cholecystitis with stones, and 28 (51.9 per cent) were for chronic conditions. These conditions included calculi either within the gallbladder or the common duct. There were only 2 operations in which stones were not involved—one for a dilated cystic-duct remnant and one for an obstructed common duct, the cause of which was not determined. If acute cholecystitis, common-duct stones and fistula formation are considered to be complications of biliary-tract disease, then 35 (67.3 per cent) of the operative procedures were of greater magnitude than those commonly associated with the surgical treatment of chronic cholecystitis with cholelithiasis (Table 1).

TABLE 1

Non-malignant Disease of the Biliary Tract in 50 Patients Aged 74 Years and Over (54 Operations)

The New York Hospital-Cornell Medical Center, September 1, 1932–September 1, 1953

Acute cholecystitis with cholelithiasis	24
Chronic cholecystitis with cholelithiasis	17
Chronic cholecystitis, cholelithiasis and choledocholithiasis	8
Chronic cholecystitis and choledocholithiasis	1
Cholecystoduodenal fistula and choledocholithiasis	1
Choledocholithiasis	1
Common-duct obstruction of unknown cause	1
Cystic-duct remnant without calculi	1
Total	*54*

TABLE 2

Incidence of Concurrent Disease in 50 Patients Aged 74 Years and Over with Non-malignant Biliary-tract Disease

The New York Hospital-Cornell Medical Center, September 1, 1932–September 1, 1953

Arteriosclerotic heart disease	26
Left bundle-branch block	5
Hypertensive cardiovascular disease	17
Generalized arteriosclerosis	15
Pulmonary emphysema	9
Diverticulitis of the colon	7
Chronic renal disease	4
Cardiac decompensation	3
Diabetes mellitus	2
Miscellaneous	13
Total	*101*

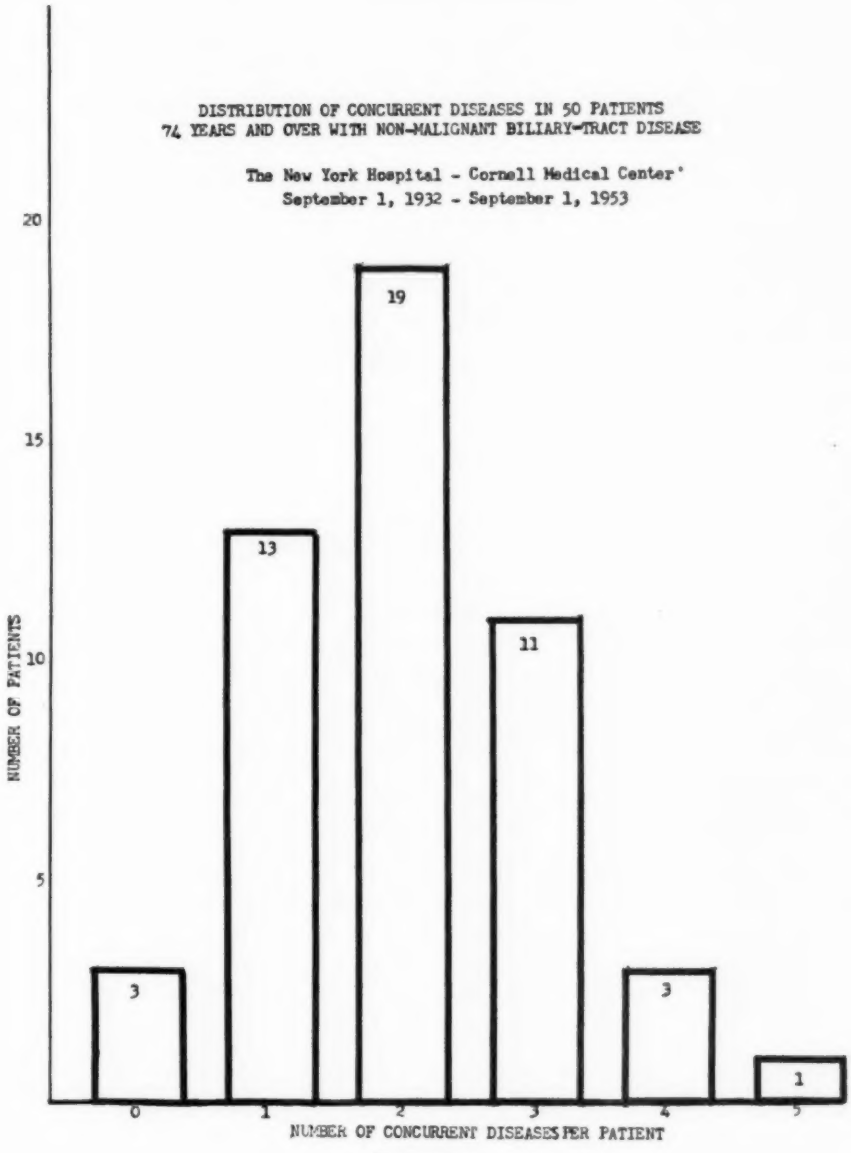

FIGURE 1

The incidence of concurrent degenerative diseases was high in these 50 patients (Table 2 and Fig. 1). The great preponderance of degenerative changes in the cardiopulmonary systems in the aged was readily apparent.

Cholecystectomy was performed in 44.4 per cent of the operations, cholecystostomy in 29.6 per cent, cholecystectomy and choledochotomy in 16.7 per cent, and miscellaneous procedures in 9.3 per cent (Table 3).

There were 7 postoperative complications following 48 surgical procedures carried out in the 44 patients who survived—an operative morbidity of 14.6 per

TABLE 3

Procedures in 54 Operations Performed on 50 Patients Aged 74 Years and Over with Non-malignant Biliary-tract Disease

The New York Hospital-Cornell Medical Center, September 1, 1932–September 1, 1953

Operation	Number	Deaths
Cholecystectomy	24	2
Cholecystostomy	16	2
Cholecystectomy and choledochotomy	9	
Choledochotomy	1	
Cholecystectomy and cholangiogram	1	
Excision of cystic-duct remnant and choledochotomy	1	
Excision of cholecysto-duodenal fistula, cholecystectomy and choledochotomy	1	1
Cholecysto-enterostomy	1	1
Totals	*54*	*6*

TABLE 4

Complications in 44 Survivors (48 Operations) of 50 Patients Aged 74 Years and Over with Non-malignant Biliary-tract Disease

The New York Hospital-Cornell Medical Center, September 1, 1932–September 1, 1953

Auricular fibrillation	2
Pulmonary infarct	1
Pneumonia	1
Wound infection	1
Cystitis	1
Thrombophlebitis	1
Total	*7*

cent. The complications are listed in Table 4. Six deaths occurred in this series—an operative mortality of 11.1 per cent. The causes of death are listed in Table 5.

PREOPERATIVE PREPARATION

Proper preoperative preparation begins by obtaining a complete medical history and a physical examination. Essential laboratory studies include: a complete blood count, a urinalysis, a blood urea nitrogen determination, a chest roentgenogram, and an electrocardiogram. The results of these may suggest the need for further investigation. The length of time that can be spent in the evaluation and preparation of each patient is determined by the severity of the illness. When immediate surgical intervention is indicated, preoperative preparation must be rapid and yet thorough, for the operative mortality is greatest in this group of patients.

In the aged individual, a low blood volume is frequently encountered. Further

TABLE 5

Data on 6 Postoperative Deaths Occurring in 50 Patients Aged 74 Years and Over with Non-malignant Biliary-tract Disease

The New York Hospital-Cornell Medical Center, September 1, 1932–September 1, 1953

Sex	Age	Duration of Attack	Jaundice	Operative Findings	Operation	Cause of Death
1. M	80	4 days	+	Chronic cholecystitis	Cholecystostomy	Friedlander's pneumonia
2. F	76	3 days	+	Cholecysto - duodenal fistula; choledocholithiasis	Repair of cholecysto-duodenal fistula; cholecystectomy; choledochotomy	Acute yellow atrophy of the liver
3. M	78	1 day	0	Acute cholecystitis with cholelithiasis	Cholecystostomy	Cerebral hemorrhage
4. F	81	3 wks.	+	Chronic cholecystitis with cholelithiasis	Cholecystoenterostomy	Cirrhosis of the liver
5. F	77	—	0	Chronic cholecystitis with cholelithiasis	Cholecystectomy	Coronary occlusion
6. F	78	4 days	0	Acute cholecystitis with cholelithiasis	Cholecystectomy	Renal failure

depletion associated with an operative procedure may result in severe and even irreversible hypotension, since the arteriosclerotic vascular system may not be able to compensate for the acute blood loss. In addition, relatively mild anoxia occurring in the presence of a diminished red-cell mass may result in severe damage to vital tissues (3). Normal hematocrit and serum protein levels do not exclude the possibility of a blood deficit. Thus, whenever possible preoperative determinations of the blood volume should be obtained on all aged patients and any deficiencies should be corrected prior to operation.

Abnormal fluid and electrolyte losses are prone to occur in acute biliary-tract disease. Deficiencies are to be recognized by clinical evaluation and appropriate laboratory studies. Fluid and salt deficits may be estimated by noting tissue turgor and dryness of the tongue, by considering the degree and duration of impaired intake, and by estimating the amount of insensible and abnormal losses. If kidney function is impaired, an excessive amount of sodium may be lost in the urine. Since low myocardial reserve is common in the aged, parenteral fluids and electrolytes should be administered with caution, in order to avoid congestive heart failure. Ziffren and Sheets (4) have emphasized that great care must be taken to avoid overcorrection of salt loss and that replacement should take place over a period of two or three days. They also point out that patients with peripheral edema due to cardiac failure may be dehydrated. Since the edema fluid has a considerable electrolyte content, such patients should be given 5 per cent glucose in distilled water to correct dehydration.

Degenerative disease processes, so often encountered in aged individuals, are the cause of many postoperative complications and deaths (5). This is particularly true for degenerative changes in the cardiopulmonary systems. Better control of these concurrent factors will result in a significant decrease in the morbidity and mortality rates of surgical procedures performed on the biliary tract.

Many elderly persons have some impairment in myocardial reserve. In the evaluation of a patient's cardiac status, an accurate history of the patient's physical abilities prior to hospitalization is helpful. If, after examining the patient, there is any question as to whether or not mild cardiac failure is present, measurements of venous pressure and of circulation time are simple tests which aid in making an accurate diagnosis. Coller and Dobbie (6) state that following the injection of a single dose of a mercurial diuretic a patient may lose 5 to 10 pounds of previously invisible edema fluid.

If there is marked congestive heart failure, elective surgery should be postponed until at least one month after the cardiac decompensation has been controlled. If diuretics have been used, determinations should be made of the blood electrolytes, for marked diuresis may cause abnormal electrolyte losses. When there is a depletion of the red-cell mass in a patient with heart disease, correction of this deficit with concentrated red-cell transfusions (whole blood from which most of the plasma has been removed) may result in considerable clinical improvement.

Unless there is definite evidence of cardiac failure, digitalis preparations should not be given. If rapid digitalization is indicated, deslanoside (Cedilanid) is probably the drug of choice. An initial dose of 0.8 mg. should be followed at three-hour intervals with doses of 0.2 mg. until a full therapeutic effect has been obtained. Overdosage may cause cardiac irritability.

Cardiac arrhythmias are best evaluated and controlled by a cardiologist. Digitalis is usually employed in the treatment of auricular fibrillation. Digitalis or quinidine sulfate may be used in the management of auricular flutter, paroxysmal auricular tachycardia and paroxysmal nodal tachycardia. Quinidine should not be used if there is known idiosyncrasy, chronic auricular fibrillation, congestive heart failure or heart block. Ventricular tachycardia is a contraindication for digitalis, and should be treated with procaine (Pronestyl).

A two to three-month interval is desirable in patients who have had an acute coronary occlusion, before any major surgical procedure is attempted.

Chronic pulmonary disease may be the cause of serious postoperative complications. Proper preoperative management is essential if respiratory distress and pulmonary infection are to be avoided. Pulmonary emphysema and chronic pulmonary fibrosis are encountered more frequently than are chronic bronchiectasis and asthma. Because the respiratory reserve is impaired, and infection may seriously aggravate the symptoms of any of these chronic pulmonary diseases, adequate control of superimposed infection should be provided for with antibiotics and measures which aid in the drainage of the tracheobronchial tree.

If time allows, oral sepsis should be corrected and smoking discontinued. Expectorants, bronchial antispasmodics and postural drainage may be employed.

Tryptar Aerosol[1], Alevaire[2] and more recently pancreatic dornase have made control of viscid secretions more effective. Barach (7) has found a solution of 5 to 10 per cent propylene glycol in distilled water, with or without a detergent, to be free of irritating side effects.

If there is an associated acute pulmonary inflammatory process, sputum cultures and antibiotic sensitivity studies of the offending organisms should be made. The correct choice of an antibiotic is an important factor in controlling the infection as quickly as possible. In general, penicillin is the drug of choice for Gram-positive organisms and Terramycin, aureomycin, Chloromycetin or streptomycin are to be used for Gram-negative bacteria. Systemic therapy may often be effectually supplemented with aerosol penicillin.

An asthmatic should be protected from as many allergens as possible. He should be kept in a single room in which no flowers or smoking are permitted. A sponge-rubber pillow should be used. Nebulized Vaponefrin and aminophylline administered orally or rectally may control the bronchospasm. If cortisone is employed, it is started in a daily divided dosage of 300 mg. The dosage is then gradually diminished to a maintenance level of 50 to 75 mg. per day. Because the administration of cortisone depresses normal adrenal function, the amount given should be increased on the day of operation to 300 mg., with progressively smaller daily doses thereafter. Fromer (8) has recommended that an infusion of 15 to 30 mg. of ACTH in 500 cc. of 5 per cent glucose in distilled water be given over each six- to eight-hour period during an acute asthmatic episode. After four days, 10 mg. of ACTH gel is given intramuscularly twice daily.

Renal function is often diminished in elderly patients. There is greater loss of function of the tubules than of the glomeruli, with a resultant impaired ability to concentrate urine and conserve body base. Prostatic hypertrophy or perineal prolapse may prevent complete emptying of the bladder. With obstruction and superimposed infection, further renal damage occurs. Preoperative evaluation of renal function should include at least two urinalyses. If the kidneys are able to concentrate urine reasonably well, they will usually tolerate a surgical procedure.

Whenever possible, operation should be avoided on patients with renal insufficiency, until there is medical control of the kidney disease. Measures to be employed include: rest with avoidance of fatigue, a diet with restriction of protein to 0.5 Gm. per kilogram of body weight per day and sodium chloride to 3 Gm. per day, and a fluid intake of 2,500 to 3,000 cc. per day as long as the urinary output is adequate. Any associated anemia should be corrected by frequent small blood transfusions. Blood electrolytes are to be maintained at normal levels. With proper care, many patients with impaired kidney function and nitrogen retention may be improved so that they will tolerate necessary operative procedures.

Liver damage is often associated with longstanding biliary-tract disease. Operations performed on patients with uncontrolled liver decompensation are

[1] A purified crystalline trypsin preparation.

[2] An oxethylated tertiary octylphenol-formaldehyde polymer.

attended by a prohibitive mortality rate. The severity of the hepatic disease and the response to treatment may be estimated by the physical findings and by serial studies of liver function. A high-caloric, high-protein diet with added vitamins is indicated. Prothrombin deficiency should be corrected with vitamin K preparations. Repeated small blood transfusions are given for anemia. Hypoproteinemia and low serum albumin levels may be improved with a high-protein diet, blood transfusions and intravenous administration of concentrated serum albumin. Limitation of physical activity and avoidance of fatigue are necessary. Restricted salt intake, diuretics and paracenteses may be required to control ascites. Every effort should be made to obtain maximum improvement in liver function prior to any surgical procedure.

The control of diabetes in a patient with chronic biliary-tract disease prior to elective surgery is usually a relatively uncomplicated problem. However, the control of diabetic acidosis in an aged individual with an acute surgical illness deserves rapid and careful treatment. It is important that the urine be examined hourly for the presence of ketone bodies and the degree of glycosuria. If necessary, an indwelling urethral catheter may be inserted into the bladder. The levels of blood glucose and carbon dioxide combining power should be ascertained initially and at intervals determined by the severity of the acidosis. These patients require varying amounts of insulin, glucose, salt and water. If the acidosis is severe 1/6 molar sodium lactate should be used in place of sodium chloride. Because large amounts of intravenous fluids are often necessary, frequent observations should be made for evidences of cardiac decompensation. A bedside venous-pressure manometer may be connected to the infusion needle through a three-way stopcock. Periodic determinations of venous pressure will aid in the early detection of a failing heart.

Evaluation of the nutritional state is an important part of the preoperative preparation. If obesity is present, a reducing regimen should be outlined and the patient carefully followed. More commonly one encounters varying degrees of malnutrition. Aged patients often lose interest in food and, along with their decreased physical activities, their appetites are diminished. Lack of teeth or ill-fitting dentures make chewing difficult. These patients should be encouraged to eat by providing attractive diets, by correcting dental problems, and by stimulation of their appetites with small amounts of wine before meals. Sustagen feedings between meals will provide added calories. In severe cases of anorexia, tube feedings may be necessary for several days in order to obtain improvement in the nutritional status. Testosterone given three times weekly in 25-mg. amounts may have a beneficial effect on protein metabolism. Vitamin deficiencies, if present, require appropriate therapy.

In recent years increasing attention has been directed towards the mental attitude of the aged patient regarding the proposed surgical treatment. When possible, it is desirable to admit elderly individuals to the hospital several days prior to the contemplated day of operation. During this interval diagnostic studies may be made, with care taken to avoid performing too many studies in too short a period of time. The patient is also given an opportunity to become

familiar with the hospital environment and to gain confidence in the hospital personnel. He should be encouraged to be up and about and to take an interest in others. The surgeon should discuss the patient's illness with him and explain what the proposed operative procedure is to accomplish. It is important that all medical personnel maintain an air of sincere optimism. Cole (9) has recommended that aged patients be given 100 mg. of ACTH daily for five or six days preoperatively. He feels that this medication stimulates their appetites and their desire to be up.

During the immediate preoperative period, arrangements should be made to have whole blood available in the operating room so that blood loss can be replaced promptly. A Levin tube should be passed into the stomach and the stomach aspirated. The tube is allowed to remain in place during the operation and for a variable period afterward. We have not used antibiotics routinely. They are used in all patients with acute cholecystitis and in those with marked pulmonary degenerative changes, in whom a superimposed infection would cause severe respiratory embarrassment. Because elderly individuals have diminished metabolic rates and because they are sensitive to depressant drugs we do not use preoperative narcotics. Small doses of barbiturates may be employed for sedation. Atropine is given one hour prior to the induction of the anesthesia in order to diminish tracheobronchial secretions. An infusion of 5 per cent glucose in distilled water is started. If the patient has diabetes, regular insulin is added to the infusion solution.

ANESTHESIA

On most occasions when cholecystostomy has been the procedure of choice, we have found local anesthesia to be quite satisfactory. When a general anesthetic is selected, ether and cyclopropane are the safest agents, since high concentrations of oxygen can be maintained with either of them. Ether is to be preferred if there is any evidence of cardiac arrhythmia. When general anesthesia is used, patency of the airway should be insured by the insertion of an endotracheal tube. This may best be accomplished under topical xylecaine anesthesia in order to decrease the amount of general anesthetic agent required. Recently, Artusio (10) has demonstrated the value of ether analgesia in poor-risk patients, particularly in those with cardiac impairment. This method allows the patient to maintain his peripheral vasomotor compensatory mechanisms during anesthesia.

OPERATIVE PROCEDURES

In the geriatric patient the surgical procedure of choice is the one that is usually the simplest and imposes the least burden. This is particularly important in emergency cases, in which the operative mortality is much greater. We have often performed cholecytostomy in the poor-risk patient with acute cholecystitis, because it permits elective cholecystectomy at a later time when the patient is not acutely ill and when there is much less risk.

Cole (9) has shown that the magnitude of the surgical procedure has a direct effect on the operative mortality. However, following cholecystectomy and chole-

dochotomy performed on patients in this age group, there has been a progressive decrease over the past ten years in the morbidity and mortality rates. The improved results are directly attributable to better methods of preparation and management.

POSTOPERATIVE CARE

At the conclusion of the surgical procedure the tracheobronchial tree should be aspirated adequately through the endotracheal tube. As the elderly patient recovers from the anesthesia his gag reflex is depressed and he may aspirate excessive secretions or regurgitated stomach contents. It is essential that the posterior nasopharynx be repeatedly aspirated with a catheter during this period. If atelectasis occurs and cannot be cleared by chest pounding and tracheal aspiration, bronchoscopy must be performed in order to remove the plugs of mucus. The patient should be turned frequently and encouraged to cough and to breathe deeply as soon as he is fully conscious. Pulmonary congestion due to excessive fluid and salt intake may cause atelectasis and pneumonitis. Narcotics are to be used cautiously and in small amounts in order to avoid oversedation and depression of the cough reflex. Small doses of barbiturates may be used for restlessness.

Fluid and electrolyte balance must be maintained. When fluids are administered parenterally, an infusion of 900 or 1,000 cc. of 5 per cent glucose in distilled water with added vitamins is given twice daily as long as the urinary output is adequate. Volume-for-volume replacement of fluid lost by drainage from the intragastric tube or from any tube placed in the biliary tract is accomplished by adding physiologic salt solution to the daily infusion while the patient is maintained on parenteral feedings. Potassium loss is replaced by the addition of appropriate amounts of potassium chloride to the infusion, as long as there is an adequate urinary output. If drainage from the tubes is marked, the electrolyte content of the fluids lost in this manner should be determined, so that replacement can be accurate. Whole blood transfusions may be necessary to correct anemia and hypoproteinemia. Concentrated serum albumin is often of considerable value in maintaining adequate albumin levels.

While in place, the intragastric tube should be under constant suction and irrigated with small quantities of saline at regular intervals in order to maintain patency of the lumen. This tube should be removed as soon as possible, for its presence limits coughing and increases the possibility of atelectasis and pneumonia. It is highly desirable to commence oral feedings as soon as practicable. Abdominal distention should be treated if it develops.

Ambulation is begun on the day of operation unless there is cardiac failure, coronary occlusion, pneumonia, peritonitis or phlebothrombosis. Early ambulation, to us, means that the patient should be up and walking about. It does not mean sitting in a chair.

While in bed, the lower extremities should be exercised. Care must be taken to avoid compression of the veins in the popliteal spaces and groin. The legs should be examined for evidences of phlebothrombosis at least twice a day. If this occurs anticoagulants may be instituted unless there is some contraindica-

tion. In selected instances superficial ligation of the femoral vein may be indicated.

If infection occurs, sensitivity studies on the offending organisms are often of value in selecting the most effective antimicrobial agent or agents, and these should be used in adequate amounts.

DISCUSSION OF DEATHS

A review of the histories of the 6 patients who failed to survive serves to illustrate many of the problems that are often encountered in the management of nonmalignant disease of the biliary tract in the aged.

Case No. 1 (*N.Y.H. #25 313*) An 80-year-old white male had had fatty-food intolerance characterized by flatulence and belching for several years. Intermittent vague abdominal discomfort had developed two months prior to admission. Six weeks later he noted jaundice, dark urine and clay-colored stools. Positive physical findings included a mild icteric color of the skin, a blood pressure of 180/90 and abdominal right upper quadrant tenderness. An x-ray gastrointestinal series showed nothing abnormal. While in the hospital the jaundice decreased and surgical intervention was decided against because of the patient's age. He was discharged but was readmitted six weeks later because of an episode of acute R.U.Q. abdominal pain and recurrent jaundice of four days' duration. An added physical finding during this admission was an enlarged liver. A cholecystostomy was performed under general anesthesia and several calculi were removed. On the fourth postoperative day the patient's temperature rose to 39° C. and remained elevated thereafter. Physical findings and x-ray evidence of a right upper lobe pneumonia were noted. The patient's condition gradually became worse and he died on the forty-fourth postoperative day. Autopsy demonstrated a marked pneumonia in the right upper lobe and a loculated abscess of the right pleural cavity due to *Klebsiella pneumoniae*.

This patient was operated upon in 1933. The complication and his death were due to infection. With the advent of antimocrobial agents, infection has played a diminishing role as a cause of death in postoperative patients.

Case No. 2 (*N.Y.H. #202 305*) A 76-year-old white woman had been well until five years before admission, when she had an attack of acute right-sided abdominal pain, nausea and vomiting. She was admitted to another hospital, where exploration revealed acute obstruction of the distal ileum due to a gallstone. Because of recurrent episodes of nausea and vomiting she was re-explored one year later at the same hospital and "adhesions about the gallbladder" were divided. She was then well until three weeks prior to her admission to The New York Hospital, when intermittent epigastric pain, belching and jaundice developed. Upon physical examination, she appeared chronically ill and was markedly jaundiced. There were two well-healed scars in the abdominal right upper quadrant, which was moderately tender. She had repeated acholic stools and her icterus index remained elevated. At operation a cholecysto-duodenal fistula was found and repaired. The gallbladder was excised and a calculus was removed from the common bile duct. Her immediate postoperative course was uncomplicated but three weeks after operation hemorrhagic cystitis developed, which persisted for three weeks. Pneumonia appeared in the right upper lobe, and then subsided. On the sixty-eighth postoperative day a wound abscess became evident and was drained. On the one hundred and tenth postoperative day she had an episode of syncope during which her pulse was barely perceptible. Following this her condition deteriorated steadily, jaundice reappeared and she expired on the one hundred and twenty-first postoperative day. Autopsy revealed acute yellow atrophy of the liver, chronic cholangitis and obstructive cirrhosis of the liver.

This patient had longstanding complicated biliary-tract disease, with consequent liver damage. The liver was damaged further by anemia secondary to the hemorrhagic cystitis,

by general debility and fever associated with pneumonia and wound infection, and finally by anoxia secondary to an episode of syncope and hypotension. The repeated hepatic insults resulted in acute yellow atrophy of the liver and death. Earlier definite treatment and improved supportive measures might well have prevented this fatality.

Case No. 3 (N.Y.H. #556 548) A 78-year-old white male was well until three years before admission when he was observed to have hypertension. He was given digitalis and remained relatively well until three months prior to admission, when he noted the onset of progressively increasing dyspnea and orthopnea. For four years he had had intermittent mild generalized abdominal pain accompanied by gaseous eructations. The episodes of abdominal distress were not related to fatty foods. Physical examination revealed a blood pressure of 190/90, an increased antero-posterior diameter of the chest with scattered wheezes and rales over both lungs, a loud precordial systolic heart murmur, and an enlarged tender liver. A chest roentgenogram showed atelectasis of the right middle lobe. On the day of admission he had an episode of cramping generalized abdominal pain, nausea and vomiting. Several hours later a right subcostal tender mass was palpated and a diagnosis of acute cholecystitis was made. A cholecystectomy was planned but because of a sudden decrease in the patient's blood pressure to 118/100 during the operation, a cholecystostomy was performed under general anesthesia. Ten hours postoperatively his blood pressure suddenly rose to 250/120. He became comatose and expired four hours later. Autopsy revealed a massive cerebral hemorrhage, generalized arteriosclerosis and pulmonary emphysema.

This patient illustrates a type of fatality that is associated with degenerative processes in the cardiovascular system. Even with great care in management, this type of death is probably unavoidable.

Case No. 4 (N.Y.H. #573 261) This 81-year-old white woman noted the onset of anorexia, nausea and right upper quadrant abdominal pain three weeks prior to admission. One week later her urine became dark and her stools became clay colored. Shortly thereafter she noted jaundice, which became progressively worse. Positive physical findings included a blood pressure of 150/100, marked jaundice, and R.U.Q. abdominal tenderness. An electrocardiogram revealed a left bundle-branch block. Results of blood studies were as follows: urea nitrogen (BUN) 23 mg. per 100 cc., serum bilirubin 33.5 units, alkaline phosphatase 6.4 units, cephalin flocculation 9 units, and thymol turbidity 9 units. Serum protein concentration and A/G ratio were normal. The patient was given vitamin K preoperatively. At operation the liver was small and cirrhotic, the head of the pancreas was hard and no common-duct stones could be demonstrated. There were three large calculi in the enlarged gallbladder; these were removed. A cholecysto-jejunostomy was performed. Postoperatively her course was one of steady deterioration. The jaundice increased and the BUN level remained elevated. She expired on the ninth postoperative day. Autopsy revealed cirrhosis of the liver, arteriolar nephrosclerosis, and toxic nephrosis.

This patient is another example of advanced liver disease in a patient with chronic biliary-tract disease. In spite of good supportive therapy before and after operation she expired because of hepatic failure.

Case No. 5 (N.Y.H. #623 940) The patient was 77-year-old white woman who noted the onset of intermittent precordial pain followed by a 60-pound weight loss and left flank pain nine months prior to admission. She was admitted to the hospital for evaluation of her weight loss. Physical examination revealed a blood pressure of 230/130, pulmonary emphysema, a precordial systolic heart murmur, and a slightly enlarged firm liver. A cholecystogram demonstrated cholelithiasis. An electrocardiogram showed coronary artery disease. A cholecystectomy and incidental appendectomy were performed under general anesthesia. In the immediate postoperative period the blood pressure remained about 118/80 and her pulse was 100. Nine hours later the patient suddenly lost consciousness, her pulse was 104 and her blood pressure was unobtainable. A diagnosis of acute myocardial infarction was made and the patient was maintained on norepinephrine for several hours before she expired. Autopsy was not obtained.

This patient had severe cardiopulmonary degenerative changes. The persistent relative hypotension in the immediate postoperative period in a patient with impaired coronary arterial circulation probably resulted in acute myocardial infarction.

Case No. 6 (*N.Y.H. #623 990*) This 78-year-old white woman had had episodes of vague abdominal pain after eating for several years. On the day prior to admission she noted the onset of more severe abdominal pain in the right upper quadrant, accompanied by nausea and vomiting. Significant physical findings included a temperature of 38.5° C., a blood pressure of 185/90, moderate pulmonary emphysema, a systolic apical heart murmur, and moderate abdominal R.U.Q. tenderness. Positive laboratory findings included albuminuria, glycosuria, acetonuria, leukocytosis, a BUN level of 12 mg. per 100 cc., CO_2 combining power 25 mEq., fasting blood sugar 303 mg. per 100 cc., serum potassium 3.7 mEq., and serum sodium 117 mEq. per liter. An electrocardiogram revealed a prolonged Q-T time which was considered as indicating an electrolyte imbalance. Following preoperative hydration with 5 per cent glucose in distilled water, a cholecystectomy was performed under general anesthesia. Postoperatively progressive oliguria developed, so that the urinary output was only 70 cc. on the third postoperative day. Thereafter the urinary output steadily improved and on the eighth postoperative day was 900 cc. However, the BUN level steadily rose to 190 mg. per 100 cc. on the eleventh postoperative day, and the patient expired. During the entire course she was maintained on a daily fluid intake which equalled the daily insensible loss plus the daily urinary output. The low blood sodium level was not completely corrected until the fifth postoperative day. Autopsy revealed ischemic nephrosis, acute and chronic pyelonephritis, intercapillary glomerulosclerosis, generalized arteriosclerosis and arteriosclerotic heart disease.

The patient had chronic renal disease with further kidney damage due to fever, electrolyte imbalance and trauma secondary to an operative procedure under general anesthesia. If the low sodium level had been corrected preoperatively and if a cholecystostomy had been performed under local anesthesia the patient might have survived.

SUMMARY

During the 21-year period, September 1, 1932 to September 1, 1953 a progressively increasing number of patients were treated surgically for nonmalignant disease of the biliary tract on the pavilion service of The New York Hospital-Cornell Medical Center.

With improved methods of preparation and management the mortality rate diminished during this period.

Further reduction in operative morbidity and mortality rates may be anticipated, as increasing attention is directed towards control of the concurrent degenerative disease processes which these patients often exhibit.

A plan of therapy for control of nonmalignant biliary-tract disease and concurrent degenerative disease processes is outlined.

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ESOPHAGEAL VARICES: CAUSES OTHER THAN CIRRHOSIS AND PORTAL-VEIN BLOCK

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Recognition of the presence of esophageal varices is important, because varices have become first in frequency among causes of fatal gastrointestinal hemorrhage. Surgical technics for portal decompression have been developed to such a degree of effectiveness and safety that in many centers they are considered the best treatment for selected patients with varices. Well recognized as bases for portal hypertension and esophageal varices are cirrhosis of the liver, extrahepatic portal-vein block, and schistosomiasis. There are other causes of varices, however. Recent large-scale use of esophagoscopic examination, which is much more efficient than roentgenologic and autopsy study for detection of varices, is beginning to show that varices may be present in several previously unexpected clinical situations.

The results of esophagoscopic experiences in the detection of varices among patients with diseases other than cirrhosis, schistosomiasis and portal-vein block are reported here. A correlation is made between the presence of varices, history of upper gastrointestinal hemorrhage, and the presence of other potential sources of hemorrhage.

MATERIAL AND METHODS

The patients were studied esophagoscopically, as the clinical situation dictated, during the course of their regular evaluation or treatment. Thus, the data were collected at random, there being no routine survey of various diseases. All patients were hospitalized and all had thorough study regarding their basic disease. Except for the pregnant women and 30 of the achalasia patients, individuals were included in this compilation only if the liver had been studied histologically, either by needle biopsy or at autopsy. All patients with the diagnosis of schistosomiasis, extrahepatic portal-vein block, or cirrhosis, including hemochromatosis, were excluded.

Examination for esophageal varices was made under 4-diameter magnification with the Eder-Hufford esophagoscope. In some patients the portal venous pressure was measured by needle puncture of the varices and open manometrics. Gastroscopic examination for gastric varices was made in 69 patients, but there was only 1 positive result.

One-hundred and sixty-six patients, classified in one of twelve disease categories, met the criteria for inclusion. Varices were found in 61. The severity of the lesions from patient to patient varied considerably, but for our purposes only presence or absence was considered pertinent. Thus, in some cases the lesions were of minimal diameter and extent.

TABLE –

	Acute hepatitis	Portal fibrosis	Fatty liver	Amebic hepatitis	Sarcoid	Cystic disease	Hemosiderosis	Metastatic disease	Achalasia	Cardiac failure	Pregnancy	Idiopathic varices
No. of patients	21	33	17	2	8	1	7	15	33	10	6	—
No. with hematemesis	2	11	8	0	1	0	0	2	11	3	1	9
Esoph. varices												
Esophagoscopy	11	13	4	1	0	1	2	3	3	6	4	13
X-ray	0	0	0	0	0	0	0	0	0	2	0	3
Portal pressure												
No. measured	0	4	1	1	0	0	0	1	0	1	1	2
Av. (mm.H_2O)		252	200	285				280		460	310	325
Other potential sources of hemorrh.												
Gastric ulcer		2	2							2		
Duoden. ulcer		8	2		1		1		2	1		2
Hiatus hernia		1	2				1					3
Esophagitis			1						33		1	33
Erosive gastritis	3	2										

PRIMARY LIVER DISEASE

Acute viral hepatitis

Study of the esophagus during the course of acute hepatitis seems particularly important for elucidation of the natural history of portal hypertension and varices. It has been assumed in the past that a long-standing head of portal hypertension is necessary before the native venous connections across the gastro-esophageal junction develop into varices. However, examination of 21 patients during the active phase of infectious hepatitis (Table 1) showed esophageal varices in 11. Varices were found as early as six days after clinical onset of the disease. It is important to note that in 9 of the patients the severity of the varices was judged to be only mild, and all were too small to permit a satisfactory measurement of portal pressure. Perhaps for the same reason, the radiologist was not successful in demonstrating any of the lesions. Gastric varices could not be found by gastroscopic examination of 18 of the patients. Two patients vomited blood during the early part of their illness; one had a duodenal ulcer and the other seemed to demonstrate a Mallory-Weiss type of episode, since he brought up blood only after several hours of vomiting.

Portal fibrosis

Thirty-three patients with a liver-biopsy diagnosis of portal fibrosis as opposed to the perilobular fibrosis of cirrhosis, were examined, and varices were found in 13. None could be demonstrated roentgenologically. Satisfactory portal pressure determinations were obtained in 4 cases. The average pressure was 252 mm. of water—a moderate increase over the normal. Eleven patients had a history of hematemesis. Seven of these had a total of 8 possible bleeding sites other than varices. Two were examined esophagoscopically during active hemorrhage, and it was seen in both that the blood was issuing from the varices.

Fatty liver

Seventeen patients with hepatomegaly but without clinically important liver disease were found by biopsy to have significant fatty metamorphosis of the liver. Esophageal varices were found in 4 of the 17, and the portal venous pressure in 1 of these was 200 mm. of water. Although 8 patients had a history of hematemesis, it was not possible to incriminate varices in any.

Amebic hepatitis

One of 2 patients was found to have mild varices of the distal three-quarters of the organ. The pressure was 285 mm. Two examinations at intervals of a couple of days showed no change.

Polycystic disease of the liver

A 60-year old woman with polycystic disease of the liver was followed for four years, to death. Moderate-sized varices were found in the distal third of the esophagus but, in spite of the presumption that the liver disease had been present for many years, she had never had recognized bleeding from the gastrointestinal tract and died of an unrelated cause.

SECONDARY LIVER DISEASE

Sarcoidosis

On rare occasions there may be enough granulomatous involvement of the portal venous channels in sarcoidosis to produce portal hypertension by encroachment on portal blood flow (1). Eight patients with sarcoidosis and diffuse liver involvement were examined esophagoscopically, but no varices were found.

Hemosiderosis

Seven patients with a liver-biopsy diagnosis of hemosiderosis were examined. None had ever bled from the gastrointestinal tract, and in 5 the esophagus was normal. One patient with congenital non-spherocytic hemolytic icterus had varices, which repeated examinations proved to be stable over a period of at least five months. The other patient, a woman who had survived for 40 years with thalassemia major, had mild esophageal varices. She had had a splenectomy in the past, which would be expected to reduce her portal venous volume slightly.

Metastatic malignancy of the liver

Fifteen patients without coexisting cirrhosis were examined. In all, physical examination at the time of esophagoscopy suggested a large amount of tumor growth in the liver. Two patients whose primary tumor was not in the gastrointestinal tract were treated for upper gastrointestinal hemorrhage. Both of these patients had esophageal varices and, as found later at autopsy, no other potential bleeding lesion. The portal pressure in one was 280 mm. Hemorrhage was believed to have been due to varices. Varices were found in only 1 other patient, a man with lymphosarcomatosis. He had had no hemorrhage during

eight years of proven sarcomatosis. At autopsy very large varices could be demonstrated throughout his esophagus.

NON-HEPATIC CONDITIONS

Achalasia

During the routine esophagoscopic study of 33 patients with achalasia, we were surprised to find esophageal varices in 3. The lesions in all were narrow and only the distal third or less of the esophagus was involved, although, because all patients had erosive esophagitis when first examined, exact mensuration was difficult. It was believed that this esophagitis had been the cause of the regurgitation of blood reported by 11 patients, because there had been no sustained bleeding, as one might expect from varices. On histologic examination, liver structure in the 3 patients with varices was normal, and no ready explanation for the lesions was apparent.

Chronic heart failure

It is well known that chronic passive congestion of the liver, which is secondary to chronic heart failure, predisposes to formation of hepatic fibrosis and at times to development of true cirrhosis (2). Pathologists have pointed out for years that patients dying with chronic heart failure may at times be found at autopsy to have esophageal varices (3–5). It has generally been assumed that such lesions develop only after there has been progression to "cardiac cirrhosis." At the bedside of the cardiac patient, however, the possibility of varices and the danger of sudden hemorrhage is easily forgotten.

Varices were found esophagoscopically in 6 of 10 chronic cardiac patients in whom liver biopsies showed no more than chronic passive congestion with minimal portal fibrosis and fat. In 1, the portal pressure was 460 mm. In 2, the varices were detected roentgenologically. We have found these dilated veins in other cardiac patients who had cirrhosis, but cirrhotics were not considered in this series.

Three of the 10 patients were admitted to the hospital because of massive hematemesis. One was examined thoroughly during hemorrhage, and the bleeding was found to be of variceal origin. In the other 2, bleeding had stopped at the time of admission, but in 1 the source of bleeding was considered to have been varices. Blood replacement was a very difficult problem in all, because of pulmonary intolerance to increases in circulatory volume, even in the face of severe anemia.

A notable finding among the cardiac patients was that the largest varices regularly occurred in the middle portion of the esophagus, rather than in the distal portion, as is always the case in cirrhosis. We can offer no explanation, but believe that this arrangement may compromise the effectiveness of pneumatic tamponade for the control of hemorrhage.

More information is needed about varices and portal hypertension in the cardiac patient, but it will be difficult to compile because the contraindications to esophagoscopy are particularly rigid in this class of patients.

Pregnancy

Various circumstances unrelated to portal hypertension led to esophagoscopic examination of 6 women during the second half of pregnancy. Varices of rather large size were found in 4. Portal pressure in 1 patient was 310 mm. Only 1 patient was studied because of hemorrhage, but she was found to have esophagitis, rather than varices.

We believe that esophageal varices of pregnancy are temporary lesions, although we have not made postpartum examinations in the affected women. They might develop in response to the same hydrostatic forces which are the cause of the development of hemorrhoids in pregnancy. Certainly, they rarely become of clinical importance.

Idiopathic varices

During the course of several years' experience in the Gastroenterology Clinics of three university-affiliated hospitals in Washington, we have observed 13 instances of esophageal varices in patients in whom we could find no cause. All patients were studied in detail specifically for an answer to varix etiology but no answer could be found. The varices in this group were considered to be of particular importance, as 9 of these 13 patients came under medical surveillance because of recent hematemesis. In the final analysis, it was believed that varices had been the source of the hemorrhage in 7 patients. One of 6 examined gastroscopically had gastric varices. Portal pressures in 2 patients were found to be 290 mm. and 360 mm., respectively.

It may possibly be significant that 8 of the patients had erosive esophagitis, 2 had pulmonary emphysema, and 1 was a chronic asthmatic. None of these diseases is known to give rise to varices, yet the high incidence of esophagitis and the usual alteration of vascular dynamics in chronic pulmonary diseases suggest associations.

CONCLUSIONS

In cases of upper gastrointestinal hemorrhage, it is necessary to consider the possibility of esophageal varices as the cause, even though there is nothing to suggest the presence of cirrhosis or portal-vein block. An expanding experience with endoscopic examination of the esophagus, with the indispensable help of telescopic magnification, has demonstrated that esophageal varices occur in many clinical situations not hithertofore suspected of being accompanied by portal hypertension. Several types of liver disease other than cirrhosis can produce varices. These lesions may develop quickly after the onset of acute hepatitis. Chronic congestive heart failure and the latter half of pregnancy appear particularly important as causes for varices, although they rarely are the source of hemorrhage in these conditions.

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CLINICAL EXPERIENCE IN RESTORING ORAL COMMUNICATION TO 274 LARYNGECTOMIZED PATIENTS BY ESOPHAGEAL VOICE*

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Maximum rehabilitation of the patient who has had a laryngectomy is determined largely by a restoration of his ability to communicate without the use of pencil and paper. To this end, the post-laryngectomy clinic at the National Hospital for Speech Disorders admitted 274 patients during the two-year period, 1952–53, for training in esophageal voice. Data obtained by a study of their case histories and by questionnaires have been subjected to critical scrutiny in order to pin-point any factors which appeared to impede the patient's progress in acquiring a satisfactory esophageal voice.

The clinic's patients routinely were instructed in groups varying from 4 to 16. Collectively, these various groups shared the following characteristics: the median age was 59 years, with an age range of 15 to 85, and most of the patients were from New York State. Only 14 women attended the clinic; in common with the majority of men, they had no more than an incomplete or complete grade-school education. Most of the patients were married and earned $5,000 or less per year. Occupationally, there was a preponderance of those who worked at unskilled jobs or were engaged in using nontechnical, specialized skills—such as house painting or driving a cab. Only about one fourth of the patients were from occupations wherein frequent and even excessive use of the voice is characteristic. By virtue of low incomes and scant savings, 51 per cent became virtually medically indigent soon after operation. They were accepted for treatment either completely free of charge, or they paid only a token clinic fee. The predominant religious affiliation was Catholic, followed by Protestants, then Hebrews.

When their doctor announced to them that the larynx required removal and they would be thus deprived of speech, almost all patients experienced various degrees of severe emotional trauma. The resultant mood was chiefly a depression. Answers on the questionnaires indicated that the most frequent emotional reactions, before and after operation, were the usual symptoms of pathologic depression—fright, anxiety, confusion, self-pity, fear of death, and insomnia. Two of the patients attempted suicide; a few others tried to convince themselves that the prospect or fact of losing the larynx did not matter very much. A third type of reaction-formation was noted among 32 patients in whom emotional attitudes developed which resembled euphoria. Following operation, the incidence of these semi-euphoric reactions almost doubled. This latter fact may be in some way related to a sense of relief, among some of the patients, that

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the more immediate mental hazard of surgery and the removal of a cancerous larynx was over.

After laryngectomy, most patients remained in the hospital between one and four weeks and registered for esophageal voice therapy within three weeks after discharge. Before surgery, many of them felt that they would surely speak again. This belief or hope was encouraged by the sick-room visits of the speech therapist from our post-laryngectomy clinic, and assumes significance when it is realized that the majority of our patients were operated upon in a single hospital in New York City, and that the therapist himself was without a larynx. Thus, by his own example, he could demonstrate visibly and audibly that surgical removal of the larynx did not mean a loss of speech forever. In contrast, other patients in our series who were visited at the hospital or elsewhere by a speech therapist who had not had a laryngectomy, reacted less favorably to reassurance.

The experience of the operation caused many to lose their previous optimism that they would speak again soon. Among those who lost hope, only a few were bitter in their conviction that the surgeon and/or the attending physician had failed to forewarn them adequately concerning the resultant inability to talk.

For most of our patients, the emotional trauma created by the laryngectomy was compounded by the consequent disruption of their economic security. Fifty-four per cent lost their jobs because they could not talk. Many others had gone to the operating room confident that their employers shared with them the expectancy of an early restoration of speech. These employers had indicated a willingness to hold open the patient's job for a few weeks. Nevertheless, as convalescence and subsequent voice therapy consumed much time, many employers for business reasons had to abandon their previous offers of sympathetic cooperation.

Only a few patients eventually were able to find new jobs; these new situations usually represented a sharp reduction of income, ego satisfaction, and the level of prestige formerly enjoyed. The patients' emotional conflicts were further amplified by concomitant dissension and despair within the family circle. It was not unusual for patients to feel that their families and friends were uncomfortable in their presence, for there was no satisfactory means of oral communication.

When we recall that the median age of our patient series was 59, it is readily appreciated that the loss of previous long-term employment, job security, and the immediate threat of possible economic disaster can act as strong potential psychodynamic factors in precipitating various involutional syndromes. That only 9 of the 274 patients had to discontinue speech therapy because of protracted and severe emotional disturbance is felt to be due, in substantial measure, to the empathic atmosphere provided by the clinic and the skilled instruction by one who had experienced a comparable ordeal.

Several of the more elderly patients have lingered indefinitely in the post-laryngectomy clinic; some of them have remained for over three years. These patients have continued to encounter difficulty in acquiring facility with esophageal voice. Although there may be numerous reasons for this circumstance, it is felt that, for them especially, the clinic setting provides an area of fellowship;

it has become an island of psychic security from an outside world of which they can no longer feel themselves a functioning part. The relative homogeneous identification offered by the group of patients who have experienced a laryngectomy operation becomes very meaningful to them. However, this psychologic advantage is somewhat nullified, because it tends to perpetuate a dependency relationship upon the clinic, and to hinder the acquirement of facility with esophageal voice.

Because of the difficulties inherent in learning to coordinate the efforts to aspirate air into the esophagus, to phonate, and to articulate, the ensuing psychologic and physiologic problems readily create an initial reaction of discouragement. Forty per cent of the patients discontinued treatment against advice. Although one-third of this group had to cease their attendance because of such factors as the need for additional surgery, medical or serious emotional complications, generalized weakness, travel distances or demise, the remaining two-thirds apparently left the clinic because of overwhelming feelings of futility regarding the possibility of ever speaking as adequately as they once did. Their subjective estimate of what constituted improvement was differently based than the objective estimate of the therapist.

These differences can be understood if we pause to identify ourselves with the speechless patient who has recently commanded unfettered oral communication. In his place, we too, would seek to talk again—just as we did before the operation—and we would grow vastly impatient with waiting. Anxiety demands gratification with utmost urgency, and anxiety pervades the patient who has had a laryngectomy and can no longer talk. To the anxiety-ridden patient who does succeed in achieving facility with esophageal voice within three to six months, even this short span of time may seem an eternity.

In spite of the emotional blocks and the physiologic difficulties arising during voice therapy, most of the patients declared that they would elect to go through it again. Only 9 of the 274 felt that the time spent in the post-laryngectomy clinic was an unrewarding experience. Rather than go through it again, they were certain that they would demand the prescription of a mechanical aid to speech, such as the electro-larynx. Another group of the treated patients (those who remained in the clinic longer than six months) were divided in their estimate of the therapeutic benefit, although 31 per cent believed that the additional time justified the results.

It has been the general policy in our clinic not to recommend the use of an electro-larynx until the therapist is convinced that the patient, for some reason, cannot possibly learn the technique for facile esophageal voice. Over the two-year period represented by the present study, only 12 patients ultimately fell into this category. It has been our experience that once the patient possesses an electro-larynx, he most likely suspends all further effort to learn to talk without the mechanical aid. In fact, the instrument was discarded by only 1 patient; after using it for ten months, he decided that he preferred to depend upon his own voice instead of the indeterminate reliability of batteries and the possibilities of mechanical failure.

CONCLUSIONS

A critical survey of the data presented in this study suggests that the simultaneous operation of several factors appears desirable, if maximum rehabilitation is to be achieved within the shortest possible time. Thus, in addition to highly skilled esophageal voice instruction, there should be supplemental psychiatric therapy and social service.

The restoration of self-confidence and self-esteem can be accelerated if the instructor's efforts are supplemented by programmed psychotherapy conducted by a trained psychiatrist. Together, the psychiatrist and the social worker can do much to buttress the shattered morale of the family's inter-personal relationships with the patient.

Much can be done to avert economic catastrophe through the institution of social service liaison with the former or prospective employer. The efforts of a social worker can help materially in educating the employer concerning the patient's problems in acquiring facility with esophageal voice technique. It should be emphasized that the average patient who has had a laryngectomy can speak well again if he is permitted adequate time for learning.

A major impediment to rapid learning of esophageal voice and rehabilitation is the severely traumatizing experience of laryngectomy, and its aftermath of speechlessness. The surgeon and the family physician have the opportunity to prepare the patient emotionally for what he must face, and to provide the hope that proper and sufficient voice training will help him to maintain his established role in society. For maximum rehabilitation of the patient who has had a laryngectomy, it appears that the team concept involving the "total push" method is fundamental.

SUMMARY

Of the 274 laryngectomized patients admitted to our hospital during the two-year period 1952–53, 110 (40.1 per cent) discontinued treatment against advice for various reasons. Because of postoperative physiologic disability or fixed emotional attitudes, 12 others (4.4 per cent) ultimately found it necessary to use a mechanical aid—the electro-larynx.

The majority of the 152 patients (55.5 per cent) who remained under instruction for three to six months, achieved facility in the use of esophageal voice. Actually, 89 of the 110 who discontinued therapy against advice were manifestly improving at the time they left the clinic. Thus, it was evident that 241 of the 274 patients admitted (88 per cent) demonstrated a capacity to acquire esophageal voice.

THE EFFECT OF ADDED CARBOHYDRATE AND FAT ON THE NITROGEN BALANCE IN THE ELDERLY

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In our earlier studies on nitrogen balance in elderly individuals (1–4) the caloric intake was kept constant as the nitrogen intake was varied from 0.35 to as much as 2.5 grams of protein per kilogram of body weight per day. It is known that in younger individuals variations in the caloric intake will influence the nitrogen balance (5, 6) and that the effect is greater in protein-depleted subjects (7, 8). In our earlier work we wished to study the effect of changes in the protein intake alone and kept the caloric intake constant at approximately 35 to 40 calories per kilogram of body weight per day. Before completing the nitrogen balance studies on a group of subjects, we thought it desirable to determine to what extent changes in the caloric intake would influence the nitrogen balance.

MATERIAL AND METHODS

The subjects used in this study were among those used in the work reported in our earlier publications. All were inmates of the St. Louis Chronic Hospital. None was suffering from acute or infectious diseases at the time of the study. There were 4 men and 5 women. The details of the physical examinations and laboratory findings will be found in previous reports. The men numbered 1 to 4 in this study are described in an earlier publication (9), in which they were numbered 1, 3, 5 and 8, respectively. Detailed data on the women may be found in another study (10), the case numbers 5 to 9 used here, corresponding to numbers 3, 4, 5, 6 and 7 in the other report.

The 4 men had been used earlier in a study of the effects of various drugs on the nitrogen balance (11). The last drug used was ACTH but a sufficient time had elapsed (several weeks) to allow the subjects to return to their normal condition before the present study was begun. One woman (No. 6) had received no therapy of any kind for several months prior to the present study. The other women had received estrogen (1 mg. of estradiol benzoate intramuscularly twice weekly) for some time in connection with other studies (12). This medication had little effect on the nitrogen balance and was not changed during the period of the tests reported here.

Initially all the subjects had been receiving a well-balanced diet containing 1.0 gram of protein per kilogram of body weight for some time. The diets, as well as the details of the collection of samples, adjustment of intake and analysis of samples were the same as in earlier studies (3). The diets were adjusted to maintain an intake of 1.0 gram of protein per kilogram of body weight per day at all times. In all of the subjects except Nos. 7 and 8 the initial caloric intake was close to 35 calories per kilogram of body weight per day. Number 7 received

approximately 42 calories per kilogram initially and No. 8 received 39 calories. The caloric intake in these 2 subjects was somewhat higher, as their weight was lower than that of the others and it was difficult to adjust both the protein intake and the caloric intake simultaneously. In all instances the caloric intake was calculated from the consumed food, by the use of the tables of Bowes and Church (13).

TABLE 1

Effect of Added Carbohydrate and Fat on Protein Balance

Subject No.	Age and Sex	Weight (Kg.)	Caloric Intake	Substance Added to Diet	Grams Protein per Day			
					Intake	Urine	Stool	Balance
1	89 M	54.1	1950	None	53.1	35.2	6.5	11.4
		56.1	2400	Carb.	56.9	37.1	9.4	10.4
		57.7	2450	Fat	57.7	38.8	8.6	10.8
2	77 M	70.4	2400	None	69.8	56.3	7.1	6.4
		71.5	2850	Carb.	72.1	53.6	7.6	10.9
		72.2	2850	Fat	72.8	55.1	8.5	9.2
3	70 M	70.2	2400	None	70.2	57.3	6.6	6.4
		71.4	2850	Carb.	72.5	55.2	8.0	9.3
		71.8	2850	Fat	72.8	52.5	7.2	12.9
4	75 M	67.6	2350	None	66.8	48.6	7.4	10.8
		69.9	2800	Carb.	70.4	48.8	7.7	13.9
		70.3	2800	Fat	71.0	51.6	8.6	10.8
5	82 F	64.4	2100	None	62.4	46.5	5.5	10.6
		66.7	2550	Carb.	65.7	42.8	8.8	14.1
		68.8	2600	Fat	68.4	47.1	6.8	14.5
		70.7	2200	None	69.8	53.0	6.3	10.8
6	68 F	58.8	2100	None	58.8	45.7	5.4	7.7
		60.3	2550	Carb.	60.5	40.8	6.9	12.8
		60.7	2550	Fat	60.9	43.3	6.3	11.3
		61.2	2150	None	60.7	46.4	7.4	6.9
7	68 F	41.5	1650	None	41.7	36.2	3.6	1.9
		41.3	2050	Carb.	42.6	30.3	8.1	4.2
		41.2	2050	Fat	42.6	30.6	6.5	5.5
		40.8	1650	None	41.2	31.1	7.0	3.1
8	80 F	48.4	1750	None	46.9	36.6	5.7	4.6
		49.3	2200	Carb.	49.3	34.1	8.5	6.7
		50.3	2200	Fat	49.5	34.9	6.8	7.8
		51.5	1800	None	49.9	37.9	6.2	5.8
9	48 F	64.6	2100	None	63.6	49.2	8.0	6.4
		65.5	2550	Carb.	66.8	44.2	8.9	13.7
		66.0	2550	Fat	66.0	45.9	9.7	10.4
		66.1	2150	None	65.4	50.0	8.6	6.8

After the initial balance period, additional food was given, equivalent to 400 calories per day in the form of carbohydrate or fat. The extra carbohydrate was chiefly in the form of sugar and sweets, with some minor adjustments in the diet. The additional fat was given in the form of extra butter and other fats and the substitution of cream for some of the milk, with a corresponding adjustment in the diet to keep the nitrogen intake at a constant level. The main portion of the food intake was therefore kept the same for each of the subjects throughout the entire period of the study and the major portion of the added fat or carbohydrate was in the form of high caloric foods of relatively simple composition. Thus, though there may have been some uncertainty as to the absolute caloric intake (inherent in calculations from tables), the increase in caloric intake was more accurately known.

The results are shown in Table 1 and are presented in a somewhat different form in Figure 1. In the table are shown, in addition to the age and sex of the subjects, the average weight, caloric intake, protein intake, output and balance during each period. Each balance period listed in the table is thirty days and all figures are averages over this time. For the male subjects the results cover three periods—an initial control period, then a period on the higher carbohydrate diet, and then a period on the higher fat diet. The female subjects were observed during these three periods and for an additional period after the fat administration had been discontinued. Diets were calculated to provide an additional 400

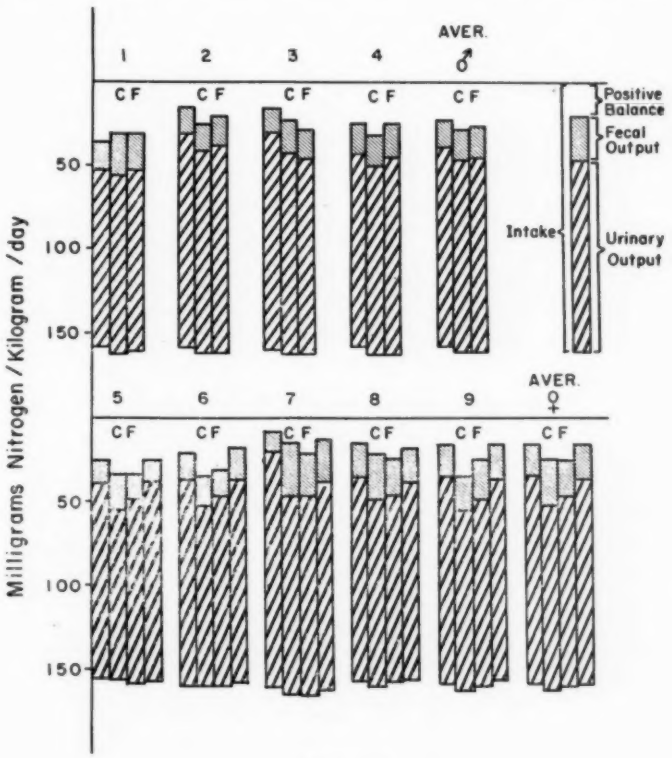

FIGURE 1

calories in the form of carbohydrate or fat. In some instances, as noted in the table, the caloric intake was actually increased by 450 calories from the first to the second period. This is due to the fact that the weight of these patients increased. Thus the increased protein intake necessary to maintain the 1.0 gram per kilogram of body weight, together with the accompanying carbohydrate and fat, increased the intake by the additional 50 calories.

The data are also plotted in Figure 1. In this figure the results are expressed in milligrams of nitrogen per kilogram of body weight per day, in order to make them more comparable among the different subjects. The method of plotting is explained by the column at the extreme right; it is the method suggested by Reifenstein (14) and used by us in a number of earlier balance studies. The columns headed C and F indicate the times when the additional carbohydrate or fat was given.

RESULTS

In all of the subjects except No. 1 there was an increased nitrogen retention during the period of added carbohydrate administration and in all except Nos. 1 and 4, increased nitrogen retention during the added fat intake. The data on the female subjects also show a return to near the initial balance after the caloric supplement was discontinued. The 2 women in whom the added carbohydrate or fat caused the greatest increase in nitrogen retention were No. 6, who received no estrogen therapy, and No. 9, who was only 48 years old (though several years postmenopausal). The average increase in nitrogen retention was greater for the women than for the men.

In most instances (Table 1) there was an actual increase in fecal nitrogen during the period of caloric supplementation. The increased nitrogen retention must then have been due to a decreased combustion of protein rather than to any increase in absorption. From our experience in previous nitrogen balance studies we would estimate that the increased nitrogen retention obtained by the increased caloric intake could also have been obtained by an increased protein intake of 5 to 10 grams per day on an isocaloric diet. At the initial levels employed (1.0 gram of protein and 35 calories per kilogram of body weight per day) an increase of 15 to 20 per cent in the caloric intake resulted in approximately the same increase in nitrogen retention as a 7 to 10 per cent increase in protein intake would have induced. The subject (No. 1) who showed no increase in nitrogen retention following the increased caloric intake was the one who initially had the greatest positive nitrogen balance (when expressed in terms of mg. per kilogram of body weight). In the other subjects there was no correlation between the initial nitrogen balance and the change with the caloric supplementation.

DISCUSSION

In elderly debilitated patients an increase in protein balance is often necessary. Though the caloric intake must be adequate, the feeding of additional calories to increase protein retention may not be desirable. A diet containing additional

fat and carbohydrate is often easier to obtain and more in line with the patient's previous dietary habits than a diet containing additional protein. The nutritional requirements for protein depend upon several factors, and treatment must be individualized. The hormonal balance is of particular importance. Deficiencies in sex hormone production may result in increased protein requirements (15). Any physiologic stress also results in decreased protein retention, especially in the elderly (11). In adjusting the diet for protein retention, after the foregoing factors have been corrected, an adequate protein intake is of greatest importance. Although the diet should be well balanced, extra fat and carbohydrate are not advisable. In our diet containing an intake of 1 gram of protein per kilogram of body weight, approximately 40 per cent of the caloric intake was derived from fats, approximately 45 per cent from carbohydrates, and the balance from protein. In our experience, elderly patients do not tolerate large amounts of carbohydrates satisfactorily, particularly when given in the form of sweets or other foods in which they are in large proportion. Whatever the exact role of fat intake in the development of atherosclerosis (to which all elderly people are subject, in a greater or lesser degree) an excessive fat intake in the elderly is undesirable (16). Accordingly, though a caloric intake which exceeds optimum requirements may result in increased protein retention, it is preferable, if dietary means are required, to increase the protein intake rather than the caloric intake.

SUMMARY

The effect of added carbohydrate or fat on the nitrogen balance was studied in 4 elderly men and 5 elderly women. All the subjects were initially ingesting 1.0 gram of protein and 35 to 40 calories per kilogram of body weight per day, and the nitrogen balance was positive. Four hundred additional calories per day in the form of carbohydrate or fat caused an increased nitrogen retention in most of the subjects, estimated to be equivalent to the retention caused by an increase of 5 to 10 grams of protein per day in an isocaloric diet. Though additional carbohydrate or fat intake has some protein-sparing action in elderly subjects, it is suggested that whenever possible, increasing the protein intake is a more satisfactory way of increasing nitrogen retention.

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THE EFFECT OF PROLONGED ADMINISTRATION OF AMMONIUM CHLORIDE ON THE BLOOD ACID-BASE EQUILIBRIUM OF GERIATRIC SUBJECTS

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It has been suggested that diminution in renal function may occur to a significant degree in aged individuals. The earlier studies of Lewis and Alving (1) and Binet *et al.* (2) indicated reduction in the urea clearance, elevation of the blood urea nitrogen level, and decline in the concentrating ability and depression of phenolsulphonphthalein excretion in males over the age of 65. All subjects studied in this age group had intrinsic renal or urinary-tract disease, as indicated by the presence of albuminuria, cellular elements in the urine, or hypertrophy of the prostate. Hypertrophy of the prostate alone, in the absence of significant urinary obstruction or superimposed infection does not necessarily lead to impairment of renal function (3); impairment occurs, however, when prostatic enlargement is of advanced degree (4).

More recent studies with patients selected to exclude intrinsic and extrinsic renal disease as well as cardiovascular disease, have shown impairment in such discrete renal functions as glomerular filtration rate, renal plasma flow, and tubular excretory capacity (5). Since the renal extraction of para-aminohippurate was intact in these older individuals, it was concluded that the observed changes in function were probably mainly due to a diminution in the effective vascular supply to the kidney, with subsequent diminution in the number of functioning nephron units, rather than to any selective impairment in tubular function (6).

This concept was questioned later by Miller and Shock (7), who found significant diminution in the response of the aged kidney to the antidiuretic hormone. These studies indicated that in the individual over 65 years of age who was otherwise normal, there was a selective impairment in the capacity of the distal tubule to perform osmotic work.

Furthermore, although the kidney is able to maintain normal blood acid-base equilibrium in geriatric subjects, it has been noted that there is a diminution in the ability to acidify the urine when an acid load is administered (8). Since these experiments were acute and merely indicated a lag in the response of the aged kidney to acid administration, it seemed important to examine the renal acidifying mechanism under the circumstances of prolonged acid administration. This is particularly pertinent in view of the widespread use of acidifying salts as diuretic agents in the treatment of the aged with chronic cardiac disease. Moreover, it has been shown that continuous and prolonged, rather than intermittent administration of ammonium chloride is more effective in potentiating

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the diuretic action of mercurials (9, 10). Accordingly, it was considered desirable to determine whether there is any diminution in the acidifying mechanism of the "normal" aged kidney.

SUBJECTS AND METHODS

Tests were made on a group of 6 males between the ages of 17 and 38 (control group) and 5 males and 1 female between the ages of 65 and 73. The subjects were selected from the wards of St. Luke's Hospital on the basis of the following characteristics: 1) freedom from clinical signs of cardiovascular or renal disease, 2) clinical history indicating no pre-existing renal or cardiovascular disease, 3) blood pressures not exceeding 150 mm.Hg systolic and 90 mm.Hg diastolic, 4) no albumin, red cells, white cells, sugar or casts in the urine, 5) no evidence of prostatic obstruction, and 6) normal values for fasting blood sugar (FBS), blood urea nitrogen (BUN), maximal urea clearance, and phenolsulphonphthalein (PSP) excretion.

All subjects received a standard hospital ward diet. Control observations of blood acid-base equilibrium were made in each instance. Ammonium chloride (uncoated tablets) was then administered in a dosage of 1.5 mEq./Kg. of body weight per day for from four to fourteen days. The tablets were administered three times a day with meals in all cases. Blood samples were collected frequently during this interval of acid administration. Upon discontinuance of the acid, satisfactory recovery values of blood acid-base balance were obtained in most instances in which compensation had not occurred during the period of acid intake.

Heparinized arterialized venous blood was sampled anaerobically under resting conditions by the method of Davenport (11). The pH of whole blood was measured at room temperature by means of a Beckman model G pH meter. Appropriate correction to body temperature was made by subtracting 0.014 pH units per degree centigrade difference between room and body temperatures. Total carbon dioxide content of plasma was determined by the manometric technique of Van Slyke and Neill (12). The bicarbonate concentration in the plasma (HCO_3^-) was calculated by means of the Henderson-Hasselbach equation. A pK of 6.1 for carbonic acid was used in this calculation.

RESULTS

In Table 1 the age, clinical diagnosis, and results of renal function tests are recorded for all subjects studied. All tests and experimental procedures were performed when the patients were convalescent or in a state ready for discharge from the hospital. There were no differences in renal function between the two groups that could be detected by the type of function tests employed. Urea clearances, PSP excretions and results of urinary analyses were within normal limits in every instance.

The blood-acid base equilibria of the two groups of subjects are tabulated in Table 2. Without exception pH and bicarbonate (HCO_3^-) values were within

TABLE 1

Clinical Data and Renal Function Tests

Patient	Age	Diagnosis*	Urea Clearance (% of normal)	PSP Excretion (% in 2 hrs.)	BUN (mg./100 ml.)	Proteinuria	Urinary Sediment
R. W.	36	Hepatitis	84	87	8.0	0	Neg.
M. L.	31	Pneumonia	100	71	13.0	0	Neg.
C. N.	25	Hepatitis	110	76	7.5	0	Neg.
E. G.	22	Bronchopneumonia	—	76	10.0	0	Neg.
C. O.	38	Rheumatoid arthritis	94	73	6.5	0	Neg.
B. M.	17	Hepatitis	93	75	12.5	0	Neg.
G. H.	70	Thrombophlebitis	80	90	13.5	0	Neg.
O. N.	69	Bronchopneumonia	89	67	10.5	0	Neg.
B. H.	73	Bronchopneumonia	100	73	11.0	0	Neg.
R. M.	67	Bronchopneumonia	89	65	10.0	0	Neg.
C. P.	65	Bronchopneumonia	136	76	10.0	0	Neg.
H. M.	65	Cerebral thrombosis	104	70	16.2	0	Neg.

* All patients convalescent at time of study.

normal limits in all individuals during control observation before institution of ammonium chloride administration (pH range, 7.37 to 7.43; HCO_3^- range, 23.2 to 29.2 mEq./L).

During the period of acid ingestion a decided difference in blood acid-base response was noted. The young individuals were able to compensate efficiently enough to the extent that pH and HCO_3^- values returned to normal within four to seven days. Values in Subject C. N. had become normal on the fourth day of acid loading, in Subject C. O. on the fifth day, in Subjects R. W., M. L. and E. G. on the sixth day, and in Subject B. M. on the seventh day. The average time of compensation for this group was 5.7 days.

Those over 65 years of age receiving the same dose of ammonium chloride appeared unable to overcome the induced metabolic acidosis and accordingly blood pH and plasma HCO_3^- values remained depressed for as long as the acid salt was administered (eleven to fourteen days). In addition, the degree of acidosis induced was more severe in the geriatric subjects. In Table 3 the maximal deviations from control values in blood pH and plasma HCO_3^- are seen to average -0.05 pH units and -3.1 mEq./L of HCO_3^- in the young group, as opposed to a fall in pH and HCO_3^- of 0.09 units and 5.7 mEq./L, respectively, in the aged group.

Upon cessation of acid loading, blood acid-base balance returned to normal in 4 of the 6 previously decompensated geriatric subjects (Table 2). Recovery values were not obtained in 2 geriatric subjects (C.P. and O.N.).

There was no evidence of gastric irritation or other adverse effects in any patient during administration of ammonium chloride. It should be pointed out, however, that with the dosage employed (1.5 mEq. per Kg.) the total daily dose of NH_4Cl did not exceed 6.0 grams in any subject.

TABLE 2

Blood Acid-Base Equilibria in Young and Aged Individuals Receiving 1.5 mEq. of NH_4Cl per Kg. Body Weight per Day

Patient	Age	Blood Values*	Control	Day of NH_4Cl Administration											Recovery**
				4	5	6	7	8	9	10	11	12	13	14	
R. W.	36	pH	7.39	7.34		7.39									
		HCO_3^-	24.4	22.9		24.7									
M. L.	31	pH	7.39	7.30		7.36									
		HCO_3^-	29.2	24.1		27.5									
C. N.	25	pH	7.41	7.40											
		HCO_3^-	24.8	23.6											
E. G.	22	pH	7.40	7.31		7.41									
		HCO_3^-	29.0	23.2		29.8									
C. O.	38	pH	7.37	7.37	7.36										
		HCO_3^-	24.2	23.6	24.6										
B. M.	17	pH	7.38	7.33			7.38								
		HCO_3^-	27.7	22.9			26.1								
G. H.	70	pH	7.39	7.32				7.34			7.31				7.38
		HCO_3^-	23.2	19.9				19.0			19.1				26.0
O. N.	69	pH	7.42	7.33				7.30			7.33				
		HCO_3^-	25.0	20.7				20.3			21.4				
B. H.	73	pH	7.42		7.32			7.29		7.33		7.32		7.33	7.40
		HCO_3^-	27.0		22.9			20.9		18.4		20.9		18.6	27.8
R. M.	67	pH	7.38			7.33			7.32			7.32			7.39
		HCO_3^-	27.5			23.0			22.6			22.7			27.7
H. M.	65	pH	7.43	7.35										7.37	7.42
		HCO_3^-	23.6	17.4				18.9†						20.1	25.2
C. P.	65	Total CO_2†	30.3	25.4		24.8		25.6				25.5			

* pH of whole blood; HCO_3^- conc. of plasma in mEq./L.
** Recovery values six days after stopping NH_4Cl administration.
† Plasma CO_2 content in mEq./L.

TABLE 3

Maximal Acid Deviations in Blood Equilibrium While Subject was Receiving NH_4Cl

Patient	Age	pH	HCO_3^- (mEq./L.)
R. W.	36	−0.05	−1.5
M. L.	31	−0.09	−5.1
C. N.	25	−0.01	−1.2
E. G.	22	−0.09	−5.8
C. O.	38	−0.01	−0.6
B. M.	17	−0.05	−4.8
Average		*−0.05*	*−3.1*
G. H.	70	−0.08	−4.1
O. N.	69	−0.12	−4.7
B. H.	73	−0.13	−8.6
R. M.	67	−0.06	−4.9
C. P.	65		−5.5*
H. M.	65	−0.08	−6.2
Average		*−0.09*	*−5.7*

* Total CO_2.

DISCUSSION

The results clearly indicate a diminution in the renal acidifying mechanism of the geriatric subjects aged 65 and over. A state of metabolic acidosis persisted in this group for as long as ammonium chloride was administered—an average time of 12.3 days (range, 11–14 days). However, in the younger group (40 years and under) complete compensation of blood acid-base balance following the standard acid load occurred in an average time of 5.7 days (range, 4–7 days). It should be emphasized again that all subjects were free of the usual clinical evidences of intrinsic or extrinsic renal disease. The implications are important, since many patients in the older age category may have indications for the therapeutic administration of acidifying salts. When these agents are prescribed, it is advisable to check frequently on the blood carbon dioxide content. When values drop below 20 mEq./L (44 vol. per cent) the dosage is reduced, and if values fall below 15 mEq./L (33 vol. per cent) the administration of acid is terminated.

Since it has been shown that acidification and ammonia secretion are functions of the distal tubule and that when these functions are depressed acidosis of the extracellular fluid occurs (13), it would appear reasonable to attribute the inability of our older patients to compensate for an acid load to specific functional impairment of this distal tubular mechanism. This defect, however, is only relative and is not manifested under normal conditions. The control acid-base equilibria in every subject studied were within normal limits. It was not until the acid load was administered that any difference between the young and old groups was observed.

We were unable to detect any significant difference between the two groups as regards the usual routinely employed clinical tests of renal function. A corol-

** Recovery values six days after stopping NH_4Cl administration.
† Plasma CO_2 content in mEq./L.

lary would be the likelihood of even more impairment in the acidifying mechanism whenever the results of clinical tests were abnormal—a strong deterrent to the use of acidifying salts unless absolutely necessary. It cannot be overemphasized that frequent checks on blood CO_2 content are essential in such situations. It is important to note that none of our patients received more than 6 grams of uncoated ammonium chloride tablets per day. A larger dose might well have been expected to intensify greatly the degree of acidosis. On the other hand, equal doses of enteric-coated ammonium chloride induce little, if any, alteration in blood acid-base balance in most individuals (14). Presumably this is due to incomplete intestinal absorption of the enteric-coated tablets. For this reason we have discontinued using the enteric-coated tablets for the purpose of potentiating mercurial diuresis (9).

SUMMARY

Ammonium chloride (uncoated tablets) in a dosage of 1.5 mEq./Kg. body weight per day was administered daily for from four to fourteen days to two groups of patients free of cardiovascular and renal disease.

Six subjects were under the age of 40 years. In this group, blood acid-base equilibrium studies showed complete compensation to the acid load by the fourth to seventh day (average 5.7 days).

Six subjects were over the age of 65. In this group, blood acid-base balance remained uncompensated and a state of metabolic acidosis persisted for as long as the acid load was administered (average 12.3 days, range 11–14 days).

The degree of metabolic acidosis induced by this standard dose of ammonium chloride was of greater severity in the geriatric group than in the young group.

The implications of this inability of the geriatric individual to compensate fully for a standard acid load are discussed.

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X-RAY FINDINGS IN GERIATRIC SURVEYS

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In an effort to discover pathologic conditions which clinically and symptomatically might not be grossly apparent in a group of aging patients, relatively complete x-ray screening was carried out, together with a case history, physical examination and laboratory investigation in each case.

In a rather large number of patients significant findings were noted. Frequently such findings were not the disability which precipitated the examination, and in many instances were of such a nature that they masked the exciting cause for the primary examination. In some cases the unexpected findings were extensive enough to alter the course of treatment, and in many cases relief of these more remote symptoms led to a corresponding well being of the patient as a whole.

METHODS

A careful clinical history was taken and physical examination performed by a competent gerontologist. Complete laboratory investigations were made. When there was no conflict with laboratory procedures (as with a protein-bound iodine determination), a complete x-ray survey was carried out. The areas covered included the skull, chest, spine, long bones, hands and wrists, knees, ankles and feet, pelvis, gall bladder and gastro-intestinal tract. In some instances an excretory urogram and a hysterosalpingogram was obtained.

RESULTS

Abbreviated case histories and some of the remote findings which were deemed important in the treatment of these patients follow.

B. R. was an 81-year-old woman who was short of breath and had asthma and a severe backache. She had a typical Parkinson tremor and was somewhat demented. X-ray findings (Fig. 1) included advanced arteriosclerosis, compressed cervical discs, old compression fractures of D10–11, marked spondylolisthesis of L4 on L5, and general tufting of the digits.

H. H. was a 51-year old man who complained mainly of symptoms of angina and the male climacteric. He had a verified history of syphilis but had no particular complaints referable to his stomach. The x-ray survey (Fig. 2, A and B) showed a constant stiffening of the pylorus of the stomach, which was compatible with linitis plastica. The aorta was enlarged, and there was marked deformity of the cervical vertebrae, with fused bodies of the Klippel-Feil type predominating.

L. K. was a 46-year-old woman. She reported for examination with two gangrenous toes, marked edema of both feet and a recommendation for amputation which she had refused elsewhere. She complained of general malaise. Her scalp showed large patches of alopecia, and there had been recent development of a beard. She was a known diabetic and had a very low I.Q. The most significant x-ray finding (Fig. 3), aside from the edema and gangrene in the feet, was a pronounced sclerosis of practically all the vessels of the body. The aorta,

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FIG. 1. *Patient B. R.*, showing old compression fractures of D10 and D11. The aorta is markedly enlarged and sclerotic.

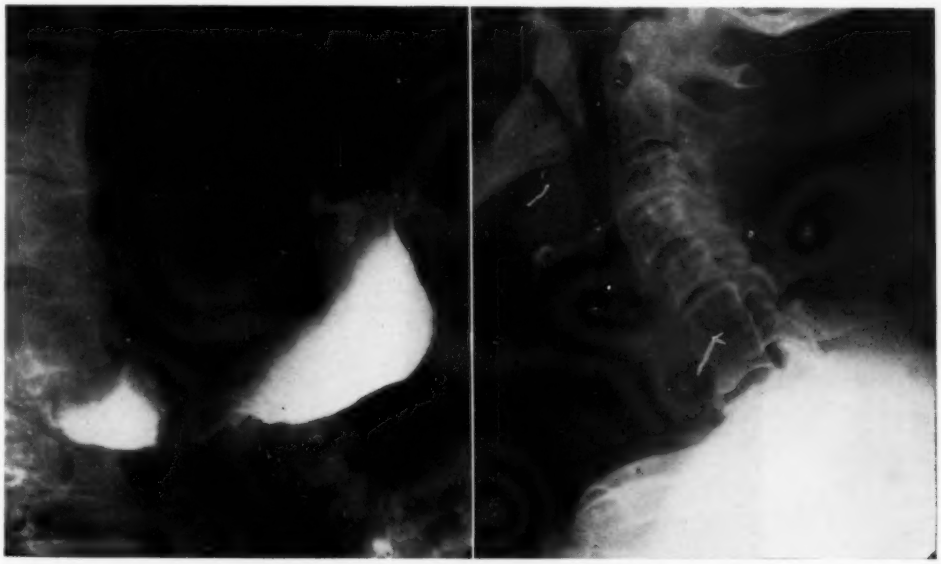

FIG. 2. *Patient H. H.* (**A**) Showing loss of pattern in the pylorus; this area was rigid during fluoroscopy, and did not balloon. The patient had a positive Wassermann reaction. The diagnosis was linitis plastica localized to the pylorus. (**B**) Showing fused cervical vertebrae, hypertrophic spurs and abnormal curve in the neck. Note demineralization of fused bodies.

and the renal and the splenic arteries were especially involved. The bones of the feet showed osteoporosis, but no osteomyelitis at the time the x-ray films were taken.

A. A. was a 62-year-old woman who complained mainly of pain in the head. She had generalized aches and pains, and was always sleepy and stuporous. She was a known diabetic.

FIG. 3. *Patient L. K.* Lateral x-ray film of stomach, showing snake-like calcifications of the vessels of the coeliac plexus above and below the pylorus. These extensive changes in the vessels were found throughout the body.

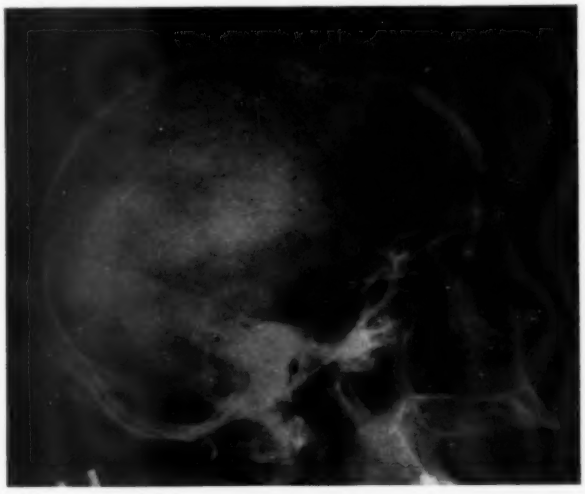

FIG. 4. *Patient A. A.*, showing marked enlargement of the sella with thinning of the posterior clinoids incident to pituitary tumor.

The x-ray films showed an enlarged sella with thinned clinoids (Fig. 4). There were frontal enostoses. Cystic bone changes were apparent in the skull and in the carpal bones. Tufting was present in the bones of the feet. A large collection of amorphous bone was noted behind the right ilium. There was a large bone cyst in the right ilium. The outstanding finding was a large destructive pituitary tumor.

FIG. 5. *Patient H. M.*, showing large collection of stones in the gallbladder. These findings were verified at operation.

FIG. 6. *Patient C. V.* Cholecystogram showing the outline of a cystic mass in the liver. The filled gallbladder overlies the spine. In subsequent urograms there was no relation between the liver cyst and the kidney. Films of the chest showed marked tenting of diaphragm.

D. J. was a 45-year-old man whose chief complaint was pain in the right shoulder. He had a history of a coronary occlusion one year earlier, and complained of some distress after eating. X-ray examination showed a hypermotility of the stomach, a duodenal diverticulum, and a malrotated colon with the entire colon lying on the left side of the abdomen, peri-

FIG. 7. *Patient G. D.*, showing marked sclerosis of one innominate bone. A small kidney stone is also visualized. The primary focus of the bone lesion was found in the prostate.

FIG. 8. *Patient G. H.* Hysterosalpingogram, showing the uterus displaced to the left side. Arrows point to walls of an ovarian cyst displacing the uterus.

tendinitis of the right shoulder, and fine gravel in the gallbladder. An old fracture of the left radius was discovered, but the patient could not recall it.

H. M. was a 72-year-old woman who had had a cerebrovascular accident and was almost completely paralyzed on the right side. She could walk with assistance, but moved around mainly in a wheel chair. One breast had been removed for carcinoma. The x-ray findings (Fig. 5) included stones in the gallbladder, sclerosis of the aorta, arthritis of the entire spine and colitis of the mucous type. Rheumatoid changes were present in the hands and there was a flexion contracture in the paralyzed hand.

C. V. was an 81-year-old man. He was nearly blind, and his chief complaint was a backache. He had had some sort of a spine affliction at the age of 17, and he had difficulty in

FIG. 9. *Patient P. C.*, showing all the loops of the colon lying on the left side of the abdomen; note fecal accumulations despite adequate preparation. Another patient, D. J., had identical findings.

walking. X-ray examination showed an old fracture of the navicular bone of the left hand. The femoral vessels were markedly sclerosed, and the aorta was markedly enlarged. There was arthritis of the entire spine and old compression fractures of D5, D10, L2 and L3, presumably not traumatic in origin. The x-ray film also showed what was assumed to be a cyst of the liver (Fig. 6).

G. D. was a 63-year-old man who had recently remarried after the death of his first wife. His chief complaint was inability to maintain an erection. The x-ray survey (Fig. 7) disclosed metastatic lesions in the wing of the left ilium and close inspection of the prostate showed the small primary node from which the metastasis occurred.

G. H. was a 51-year-old woman, typical of many in whom the x-ray survey was made. She was obese, had hot flashes, irregular menstrual periods, backaches and some degree of mental depression. The significant x-ray findings were observed in a hysterosalpingogram (Fig. 8), in which the walls of a large ovarian cyst, containing calcium, were clearly outlined. The cyst displaced the uterus to the opposite side. Unfortunately the patient was not followed.

P. C. was a 47-year-old woman who complained of a vaginal discharge and low-grade pelvic pain. She had no intestinal symptoms. She was an alcoholic. The interesting x-ray finding was malrotation of the colon (Fig. 9). The entire colon lay on the left side of the abdomen.

SUMMARY AND CONCLUSIONS

A short series of representative cases has been presented, demonstrating x-ray findings in a series of geriatric patients. In practically all cases hidden pathologic conditions were found, of which the patient was not aware. Undoubtedly these conditions were related to some of the signs and symptoms of which these patients complained during their lives.

The conclusion seems warranted that a complete, routine x-ray survey is productive of a large number of significant findings in the geriatric patient and the procedure has a high degree of merit.

TREATMENT OF THE ELDERLY HYPERTENSIVE PATIENT*

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It is a peculiar fact that for any given level of elevated blood pressure, the older the patient the better tolerated is the hypertension. Dr. Master has found that "normal" blood pressure (represented by the center of the bell-shaped distribution curve) in the aged population is above 140/90 mm. Hg. Various reports on patients in homes for the aged indicate that extremely high levels of blood pressure may be tolerated with apparent well-being in patients over 70. Although high levels of blood pressure are not uncommon in the elderly it is rare for the malignant phase of hypertension to develop in patients after the age of 70.

Systolic pressure is often disproportionately high in comparison to diastolic in the elderly, due to loss of aortic elasticity. The volume of blood ejected during systole enters a reservoir which has no resiliency, and hence the pressure rises sharply. Nevertheless, diastolic hypertension although less common also is observed, and diastolic pressures of 120 and 150 mm. Hg and even higher are not infrequent in the elderly hypertensive patient.

Another important difference between young and old hypertensive subjects is that atherosclerosis of cerebral, cardiac and renal vessels usually is well established in the older group. Often the symptomatology is the result of atherosclerosis rather than of hypertension. For example, enfeebled memory, inability to concentrate and loss of judgment in the aged hypertensive person are due more to the accompanying cerebral arteriosclerosis than to the high blood pressure. Reduction of blood pressure in such a patient often will lead to further cerebral ischemia and an intensification of symptoms rather than an improvement. This does not mean that hypertensive encephalopathy does not occur in the aged. I have seen patients in the 80's who have had severe mental disturbances on the basis of a high diastolic pressure, and who have improved after reduction of blood pressure. The choice between treatment with hypotensive procedures and no treatment requires judgment as to whether the symptoms are due to atherosclerosis primarily or to hypertension. This often can be determined only by cautious trial.

However, in view of the fact that asymptomatic hypertension is well tolerated in the aged, that cases exhibiting primarily elevation of systolic pressure reflect merely loss of aortic elasticity rather than an increased peripheral vascular resistance, and that symptoms and signs are often due to arteriosclerosis rather than to hypertension, treatment of the aged patient should be tempered by

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these considerations. Caution and discretion become the guiding principles in geriatric management.

Nevertheless, it is important to select those cases in whom some benefit may be expected, if the blood pressure is reduced. So far as geriatric medicine is concerned we could include in this category the following types: 1) Patients with diastolic pressures of 130 mm. Hg or more, and symptoms suggestive of encephalopathy, *e.g.*, occipital headaches, mental confusion or transient neurologic findings, 2) patients with diastolic pressures above 110 mm. Hg. and signs of congestive heart failure, and 3) patients with high diastolic pressures and hemorrhages and exudates or papilledema in the optic fundi. Only in the Grade IV cases, which are extremely rare after 70, is the use of ganglion-blocking drugs to be considered.

TREATMENT

Ganglion-blocking drugs

Despite the frequency of atherosclerosis in the aged it should not be thought that the vascular system is fixed, or that reduction of blood pressure is impossible or even difficult. The elderly arteriosclerotic frequently is unusually sensitive to ganglion-blocking drugs, so that relatively small dosages of hexamethonium or pentolinium may induce profound hypotension. For this reason, the use of such drugs should be avoided in patients beyond the age of 70, although these agents have great value in the younger age groups.

Rauwolfia

When reduction of blood pressure seems indicated in the elderly patient, satisfactory results usually have been obtained in this clinic either with Rauwolfia alone or, if necessary, in combination with the Veratrum alkaloids and/or Apresoline.

Reserpine is the principal active alkaloid of *Rauwolfia serpentina*. Either Rauwolfia extracts, such as Raudixin or Rauwiloid, or reserpine (Serpasil) are the easiest of all the hypotensive agents to administer because the dosage is fairly uniform and the reduction of blood pressure rarely is so profound as to induce hypotensive collapse reactions. The decrease in blood pressure is gradual and occurs over a period of days and sometimes weeks. The acute side effects are mild and include sleepiness (relieved by reducing the dosage), nasal stuffiness (usually relieved by antihistaminics either sprayed in the nose locally or given systemically) and evidence of parasympathetic activity as shown by increased appetite, bradycardia, increased gastric acidity and occasionally increased frequency of bowel movements. Although the usual mood or emotional state induced by the drug is a reduction of anxiety and increased equanimity, in a few patients the effect is unfavorable, with disturbing nightmares, lethargy or crying spells.

The most serious reaction occurs after several months or more of continuous treatment. It consists of a mental depression often to the point of active contemplation of suicide. Thus, Rauwolfia despite its usefulness, must be treated with respect. Maintenance dosage should be no higher than is necessary to con-

trol blood pressure (0.1 to 0.25 mg. of reserpine or the equivalent of the extracts per day) and the patient should be forewarned of the possibility of a depression and told to discontinue the drug if such mental symptoms should develop.

We also have seen severe epistaxis and unexplained gastrointestinal hemorrhage in patients taking reserpine, but not frequently enough to be certain that they were causally related to the medication.

Veratrum

The next group of agents under consideration are the Veratrum alkaloids. Despite occasional distressing bouts of vomiting and hypotensive reactions no deaths have been reported in the literature from the use of these agents. They are particularly useful in the aged because of this margin of safety. I recall a 79-year-old woman with a recent cerebrovascular accident who was given, by mistake, five times the recommended dose of Veriloid intramuscularly. The blood pressure became unobtainable. During the succeeding hours three injections of Neosynephrine were given at about hourly intervals to restore the blood pressure. The patient not only survived but walked out of the hospital ten days later.

Successful therapy with Veratrum (either the alkaloids of *Veratrum viride* or protoveratrine) is a "treatment by technique," in the manner of insulin treatment in the diabetic. A dose which is effective in one patient may be toxic in a second and ineffective in a third. Therefore, each subject must be "titrated" by beginning with a small dose, increased by small increments about every forty-eight hours until a significant reduction of blood pressure occurs. The dosage must be increased persistently until either the pressure falls or side effects appear. Complete reduction of the blood pressure to normotensive levels is not to be expected and probably would not even be desirable in the elderly, arteriosclerotic patient. The aim rather is to reduce a significantly elevated blood pressure to a more benign but still hypertensive range. Veratrum frequently will be successful in this purpose in the elderly hypertensive, if certain provisos are borne in mind: 1) Veratrum is more effective if combined with Rauwolfia, or with sodium amytal or phenobarbital if the patient cannot tolerate Rauwolfia. 2) Frequent recordings of the blood pressure aid dosage adjustment, but the hypotensive effect of the drug will usually not be registered when the patient is under the emotional stress of the office visit. Hence the measurements should be made under calmer circumstances. Teaching a member of the family to record the pressure in the home several times daily, and especially two or three hours after a dose of the drug, is the most practical way to handle this problem. 3) Dosages should be spaced at least six hours apart at *all* times (usually 8 A.M., 2 P.M. and 10 P.M.). If the patient sleeps late, takes the morning dose at 11 A.M., and follows with the regular 2 P.M. dose, the cumulative effect will almost certainly result in overdosage phenomena. 4) The patient is not to eat for four hours after any dose, because the ingestion of solid food at the time of maximum action of the drug may precipitate nausea and vomiting.

By utilizing these few simple techniques in management, significant hypertension often can be moderated, particularly in the older patient. Veratrum is recommended in geriatric medicine, not because of its efficiency in reducing the blood pressure to normal, but because of its safety when administered with a reasonable amount of discretion.

The final drug under consideration is 1-hydrazinophthalazine or hydralazine (Apresoline). This agent markedly reduces peripheral resistance and at the same time increases cardiac output, and total splanchnic (including renal) and cerebral blood flows. The acute side effects which consist primarily of headaches, palpitation, tachycardia and exertional dyspnea are expressions of the hemodynamic effects of the drug. They can be avoided in large measure by beginning with a small dose and increasing it gradually to effective levels. Dependent edema also is not an uncommon side effect but is seen most frequently when the drug is given in combination with ganglion-blocking agents.

The reactions occurring with continued high dosage may be quite serious and are expressions of a hypersensitivity state. They include arthritis, dermatitis and a lupus erythematosis-like syndrome. These severe reactions can be avoided almost entirely if the total daily dosage is kept below 300 mg. per day.

Like Veratrum, hydralazine is most effective when combined with other hypotensive agents. We have used it most effectively in the elderly patient as an adjunct to Rauwolfia or Veratrum therapy or to both. Our usual procedure is to try first Rauwolfia alone, then add Veratrum; if unsuccessful, Veratrum is omitted but Rauwolfia continued and hydralazine (Apresoline) added; if necessary all three are combined.

Diet

A certain amount of attention is paid to the diet in the elderly hypertensive patient. If the patient has a cardiac disorder salt is sharply restricted, but if there is no cardiac disease only moderate salt restriction is imposed. Because of the increasing evidence concerning dietary fat in the production of atherosclerosis, our patients are told to avoid dairy products except skimmed milk, butter milk and uncreamed cottage cheese, and also to avoid other sources of animal fat such as fatty meats. Whether this will produce any long-term benefits remains to be proved but it seems to be a reasonable procedure in the light of our present state of knowledge.

SUMMARY

It should be emphasized that intensive treatment of hypertension seldom is indicated in geriatric medicine. Most patients, particularly those with primarily systolic hypertension, require no special treatment. A few with an elevated diastolic blood pressure and organic complications which appear to be due to the hypertension per se, may benefit from moderate reduction of blood pressure. The drugs of choice in this special group of elderly patients are not the ganglion-blocking agents, despite their great value in younger patients, but Rauwolfia, Veratrum and hydralazine.

UNSUSPECTED CARDIAC INFARCTION WITH CEREBROVASCULAR ACCIDENTS

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Unsuspected cardiac infarction is occasionally associated with cerebrovascular accidents in elderly patients. The high incidence of arterial degenerative disease in the aged, and especially the complications involving the heart and brain, emphasize the importance of recognizing the possible coexistence of both cardiac and cerebral conditions. There is also an interesting diagnostic problem, since the cardiac lesion may be relatively "silent" in the presence of a paralytic stroke. The present study was made to determine the nature and incidence of acute myocardial infarction associated with cerebrovascular accidents during a one-year period in a large city hospital.

Simultaneous occurrence of coronary thrombosis and cerebrovascular accident has been reported sporadically in medical literature during the past twenty-five years. The incidence of acute cardiac infarction coexistent with the acute cerebrovascular condition, however, has varied considerably since it was first mentioned by Parkinson and Bedford (1) in 1928. In spite of the fact that acute coronary thrombosis may appear at the time of a cerebrovascular seizure (thrombosis, hemorrhage or embolism), some uncertainty has remained as to the frequency of simultaneous occurrence of the two conditions.

The first comprehensive work on this subject in America was published by Dozzi (2). In recent studies there has been an attempt to determine more accurately the relative frequency of combined vascular lesions of the heart and brain. The incidence of paralytic strokes in patients having coronary thrombosis has ranged from 4.9 per cent in an early clinical report (3) to 29 per cent in a later autopsy series (4). The incidence of coronary thrombosis in patients initially presenting cerebral apoplexy has not varied so widely. The latter coincidence has been reported as ranging from 10.1 per cent (5) to 15 per cent (6). A cerebrovascular lesion coexisting with coronary thrombosis may be of thrombotic, hemorrhagic or embolic type. Data concerning the time relationship between the two conditions are scant, partly because coronary thrombosis may go unrecognized during life in cases of cerebrovascular accident. In the latter condition it is therefore, important to obtain electrocardiograms when any suspicion exists as to the possibility of simultaneous cardiac infarction.

CLINICAL DATA

The present study was made to determine the incidence of acute coronary thrombosis coexistent with cerebrovascular accident at Temple University

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Hospital during the past year. All clinical records for this period were reviewed, in which either an acute myocardial infarction with or without coronary thrombosis, or an acute cerebrovascular accident (thrombosis, hemorrhage or embolism) appeared among the final diagnoses; these numbered 267. The series was limited to patients in whom acute episodes had occurred. Such diagnoses were established from clinical histories, electrocardiograms and available necropsy material.

Among the 134 cases of acute cerebrovascular accident (74 thrombosis, 53 hemorrhage, and 7 embolism), there was coexistent acute coronary occlusion in 19. In this group of 19, there were 10 deaths (5 autopsies). In the total group of 134 cases, there were 62 deaths (30 autopsies). Of the 134 patients, 81 were male and 53 female; 86 were white and 48 Negro. Ages in this series ranged from 29 to 93 years. The age distribution in decades was: 20–29, 1; 30–39, 4; 40–49, 18; 50–59, 31; 60–69, 41; 70–79, 20; 80–89, 8; and 90–99, 1. Among the 19 patients with coexistent vascular lesions, 6 were women and 13, men. Their average age was 64 years. The present series corroborated the usual finding of male preponderance in coronary heart disease and its complications. In these 19 cases, the cerebral lesions were of varying types, 15 being thrombotic, 3 hemorrhagic, and 1 embolic.

DISCUSSION AND CASE REPORTS

Cerebral hemorrhage, embolism and thrombosis commonly occur in aged persons. In this country 138,517 deaths were reported in 1949 from cerebrovascular accidents occurring in persons between 50 and 89 years of age. The greatest number occurred after the age of 55, most deaths being recorded between the ages of 60 and 84 (7).

Alvarez (8) has called attention to the fact that slight strokes constitute one of the most important illnesses of later life. Cerebral apoplexy in the aged is usually due to hemorrhage resulting from arteriosclerotic vascular changes. In a study on the duration of life after cerebrovascular accidents, Newbill (9) found that sudden death (within two hours) was unusual in the elderly. If death came within twenty-four hours after the onset of the symptoms of stroke, hemorrhage was the most likely cause. Thrombosis was much more common, however, in patients who survived more than a month after the initial episode. The average survival period after thrombosis was found to be fifteen times as long as after hemorrhage and embolism. Much depends on the location and the number of lesions in the cerebrovascular accidents. The coexistence of heart attack and paralytic stroke in 7 per cent of the present series obviously decreased the chance or duration of survival in these invididuals.

The clinical features of these 19 cases of combined cerebral-myocardial injury were of special interest. Presenting symptoms were usually neurologic in character; the cardiac symptoms were much less apparent. There were symptoms referable to both lesions in 4 cases, but neurologic findings were more

striking. In 15 cases cardiac complaints were absent. Presenting signs and symptoms in the 19 cases were as follows:

Hemiplegia	10
Unconsciousness	5
Dysarthria or aphonia	5
Chest pain	4
Hemiparesis	1
Severe vertigo	1
Marked dyspnea	1
Cardiac decompensation	1
No cardiac findings	15

Correct clinical diagnoses in cases of combined lesions of brain and heart are made only with difficulty during life, because of the obscurity of symptoms referable to cardiac disease. The latter symptoms are often masked by the predominantly neurologic picture. It is probable that combined lesions have often escaped detection, or have been misdiagnosed in the past. The increasing incidence reported in recent years has been proportional to an augmented interest in their detection.

In general, it was not possible to establish the time relationship as to which vascular lesion was antecedent in our series. Since the patient who has had a stroke is frequently unable to provide an adequate history, the necessary details are often lacking. It may be of significance that 4 patients had chest pain of substernal nature. It is possible that in these individuals, as well as in others without chest pain, a coronary occlusion had occurred. This event, precipitating a drop in blood pressure, would predispose the patient to cerebral thrombosis. In a recent study, Sturup (10) concluded that decompensated heart disease and factors causing a sudden fall in blood pressure appear in close time-relationship to strokes. In addition, the possibility of mural thrombus formation in relation to myocardial infarction introduces the hazard of cerebral embolization in some patients. On the other hand, coronary occlusion has been observed to occur shortly after cerebrovascular accidents. This may reflect again a drop in blood pressure or the generalized tendency to thrombus formation as a result of the initial acute lesion. In either of these situations, however, administration of anticoagulants should be a useful measure. The following case abstracts illustrate the necessity of being aware of these coexistent conditions:

Case #1. A 66 year-old white woman was admitted to Temple University Hospital shortly after being found by her daughter in an unresponsive condition, with an evident left hemiplegia. Past medical history included known hypertension during the previous five years, with occasional episodes of dyspnea and transient precordial pain, relieved by rest and nitroglycerine. During the week before hospitalization she had been confined to bed at home because of bronchitis with productive coughing of scant, mucoid sputum. No recent episodes of anginal distress were reported. On admission she was stuporous and unable to speak. There was flaccid paralysis of the left face and extremities, together with decreased deep tendon reflexes and Babinski's sign on that side. Scattered crepitant râles were audible over the lung bases bilaterally. The heart was not enlarged; occasional extrasystoles were

present, but no murmurs were heard. The blood pressure was 148/80. Lumbar puncture and roentgenograms of the skull showed no abnormalities. An electrocardiogram taken on admission, however, indicated an acute posterior myocardial infarction. In spite of vigilant supportive therapy, her hospital course was steadily downhill. The patient became comatose and expired one week after admission.

Case #2. A 58-year-old white male was admitted, shortly after he had collapsed on the street. There was a history of a respiratory infection causing right-sided chest pain during the previous week, for which he had been reluctant to rest as had been advised by his physician. Known diabetes mellitus for the preceding fifteen years had been regulated by diet and insulin. Right-sided pneumonia and suspected peptic ulcer had been present six years previously, but there was no history of typical anginal distress. Until shortly before entering the hospital, he had worked in a steel mill. On admission the patient was stuporous, moderately dyspneic, and had left hemiplegia. The heart was not enlarged, the rhythm was regular, but the sounds were of poor quality. No murmurs were heard. The blood pressure was 180/80. Numerous moist râles were audible at both lung bases, being more pronounced on the right side. There was a flaccid left hemiplegia, with decreased reflexes in the extremities and a Babinski sign on the left. An electrocardiogram on admission indicated a recent anterolateral myocardial infarction. Further tracings during his hospitalization confirmed this diagnosis and showed healing of the acute process. The patient was digitalized and anticoagulant therapy was given. His diabetes was adequately controlled. He improved progressively during his hospital stay, being discharged one month later with only residual left hemiplegia.

Case #3. A 64-year-old white male was admitted soon after gradual onset of difficult, slurred speech, incontinence of bowel and bladder, and weakness of the right upper extremity. These complaints followed by two days an episode of sharp precordial pain, which radiated into both arms and persisted until relieved by injections administered by his physician. Profound weakness, pallor and restlessness, but no dyspnea or unconsciousness, preceded the neurologic symptoms. The past medical history was noncontributory. There was no known hypertension or previous angina pectoris. Physical examination showed an elderly man, somewhat confused, incoherent in speech and having definite weakness of both right extremities. Heart sounds were distant, the point of maximal impulse not palpable, and there was a soft precordial systolic murmur, not transmitted. Occasional extrasystoles were noted. The blood pressure was 120/82. The lungs were essentially normal. Motor and sensory aphasias were present, together with right central facial weakness. There was flaccid weakness of the right extremities, with diminished tendon reflexes and a Babinski sign on that side. An electrocardiogram indicated acute anteroseptal myocardial infarction; serial tracings subsequently showed resolution of this acute process. The patient was started on an anticoagulant regimen, and progressively improved during his hospitalization. Speech and the right hemiparesis improved, and he was discharged two weeks after admission.

Case #4. A 48 year-old white man's chief complaint was loss of power in his right hand and leg, of sudden onset shortly before admission. There was a past history of hypertension for several years (untreated) and of occasional headaches. The most recent headache, a week before the present illness, had been in the left temporal region. There had been a peptic ulcer two years previously, but there was no history of cardiorespiratory difficulty. The family history revealed that his father had died from a stroke, and his mother from cardiorenal disease with diabetes mellitus. Examination on admission showed a conscious, cooperative man complaining of weakness in his right arm and leg. There were signs of chronic hypertensive retinopathy in the eyegrounds. The heart was moderately enlarged to the left, sounds were muffled, the rhythm was regular, and there were no murmurs. The blood pressure was 156/102. The lungs were resonant throughout. There was a right hemiparesis with slightly increased deep tendon reflexes, but no Babinski sign. Speech and sensation were unimpaired. An electrocardiogram, taken shortly after admission, showed left ventricular hypertrophy and recent posterolateral myocardial infarction. This finding

was corroborated by subsequent tracings. The patient's stay in the hospital was uneventful. He recovered considerable strength in his right extremities and returned home one week after admission.

The occurrence of coronary thrombosis in association with a cerebrovascular accident poses an interesting problem in differential diagnosis. A cerebral accident may result, for example, from recent cardiac infarction with mural thrombus formation, or from embolism to the brain from mitral stenosis, auricular fibrillation or bacterial endocarditis. Also, intracranial neoplasms, uremia and general paresis may be accompanied by cerebral hemorrhage. In all cerebrovascular lesions, therefore, examination of the ocular fundi and cerebrospinal fluid is of great importance.

It is apparent from the present study that clinical appraisal alone is not always helpful in establishing the coexistence of the two acute vascular processes. The possibility of such coexistence, however, should be routinely investigated when one is confronted by a patient with an acute cerebrovascular lesion. Friedberg (11) and Olsen (12) have recently emphasized the importance of recognizing these combined lesions of heart and brain. Race and Lisa (6) demonstrated that the diagnosis of coronary occlusion had been clinically overlooked in 1 out of every 5 cases in which autopsy was performed. There should be an increased index of suspicion regarding patients who manifest a drop in blood pressure, generalized weakness, pulmonary congestion, cyanosis and chest pain. It is possible, however, for myocardial ischemia or infarction to develop in a patient who has had a stroke, without the immediate appearance of the foregoing signs and symptoms. Therefore, electrocardiographic study is an important routine procedure in all patients with acute cerebrovascular lesions. The detection of otherwise unsuspected cardiac complications will influence the therapeutic program and may alter the prognosis.

SUMMARY AND CONCLUSIONS

1. Unsuspected cardiac infarction occasionally occurs in association with cerebrovascular accidents in elderly patients. Coexistence of these two conditions, each common in the aged, provides an interesting diagnostic problem, since the cardiac lesion may be relatively "silent" in the presence of a paralytic stroke.

2. In a review of 134 cases with diagnoses of acute cerebrovascular accident and/or acute coronary thrombosis, it was found that these two conditions coexisted in 19 patients (7.0 per cent).

3. Due to a predominant neurologic symptomatology in patients with coexistent strokes and heart attacks, the likelihood of the simultaneous occurrence of these two conditions warrants renewed emphasis. Electrocardiograms are of great diagnostic value for the detection of the heart lesion under these circumstances.

4. In the present study, the incidence of unsuspected cardiac infarction in association with cerebrovascular accident corresponded to that recently re-

ported in the literature. Four illustrative case abstracts of combined vascular lesions of heart and brain are presented.

5. Careful consideration should be given to this diagnostic entity in the older patient. It is important from a therapeutic standpoint that the possibility of its presence should be thoroughly investigated.

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RECOVERY FROM DEMENTING PSYCHOSES OF OLD AGE

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With increasing age, pathologic changes usually develop in the brain, which may become the site of arteriosclerotic processes or senile degeneration. When these changes are marked they are often associated with certain characteristic symptoms, and the combination is described under the heading of "acute or chronic brain syndrome." This disorder consists of:

1. Impairment of orientation.
2. Impairment of memory.
3. Impairment of all intellectual functions (such as comprehension, calculation, knowledge, and learning).
4. Impairment of judgment.
5. Lability and shallowness of affect (1).

When an elderly person exhibits the foregoing symptoms in marked degree and when there is no evidence of other etiologic factors, the disturbance is usually attributed to senile or arteriosclerotic changes. The patient may then be said to have "senile dementia," a "senile psychosis," or an "arteriosclerotic psychosis." More recently these conditions have been designated "chronic brain syndrome associated with cerebral arteriosclerosis" or "chronic brain syndrome associated with senile brain disease" (1).

When one of these diagnoses was made in the past, the patient's condition was usually viewed as irreversible. Such a conviction naturally influenced therapeutic measures, which often became dominated by pessimistic attitudes. Admittedly the underlying senile and arteriosclerotic changes are not reversible by present methods of treatment. However, these organic changes are not the only factors of significance in the origin of the brain syndromes in older people (2, 3).

The reversibility of the non-dementing psychoses of old age has been adequately demonstrated by the successful treatment of affective and paranoid psychoses in elderly persons by electric-shock therapy (4–6). Such studies demonstrate that these types of psychoses in elderly people do not arise from the irreversible damage of degenerative brain disease.

But there is a need also to view dynamically the dementing psychoses of old age, because these similarly show no clear relationship between the severity and duration of symptoms and the extent of anatomic changes in the brain. The extent of pathologic changes found postmortem bears no predictable relationship to the degree of mental impairment shown during life. Widespread arteriosclerotic and senile changes may be found in the brains of persons who, during life, showed excellent mental functioning. Conversely, persons with the symptoms of chronic brain syndrome leading to such diagnoses as "senile psy-

chosis" or "arteriosclerotic psychosis," may be found at autopsy to have brains with relatively few degenerative changes (7–10). Clearly other factors must enter into the causation of these psychoses of old age. More plastic factors of both intrinsic and extrinsic origin must be considered.

In the first place, the capacity to compensate for a loss of function may be more important than the loss of the function (8, 11–13). This compensatory capacity is an expression of all the adaptive resources developed by the personality in earlier years. Some evidence indicates that persons who have adapted poorly to earlier life situations (3), or who have been unable to maintain "social integration" (*i.e.*, close personal relationships) in old age (14), are more susceptible to senile psychoses than are persons who have adapted well to earlier stresses and maintained close personal relationships.

The capacity for compensation itself is a dynamic function capable of fluctuating according to circumstances. Stressful situations, whether the stress is physical or psychologic, may impede the capacity to compensate for loss of cerebral function and thus precipitate a psychosis in someone who had previously compensated adequately. The stress may operate at a purely physical level by further damaging the brain, as during infectious diseases or nutritional deficiencies (2). On the other hand, it may operate at a psychologic level through changing the attitudes and feelings of the patient and impairing his interest in life, thus promoting a collapse of efforts to adapt to reality. External stresses are apparently more significant in the origin of senile psychoses than of arteriosclerotic psychoses (14), but cannot be neglected in either group.

Failure to appreciate the dynamic factors in the dementing psychoses of old age, and a concomitant preoccupation with the irreversible structural changes, may lead to oversight of important therapeutic measures. To illustrate the importance of extrinsic stresses in these psychoses we describe 5 patients in whom symptoms clearly indicative of senile or arteriosclerotic psychoses occurred. In each case these symptoms subsided, either with removal of an important stress or stresses, or with a diminution in the force of the stress brought about by psychotherapeutic measures or by the passage of time.

CASE REPORTS

1. A well known, 80-year-old physician, a life-long bachelor, following retirement from an academic position on account of age, began to take less and less interest in life. He spent most of his time reading in his apartment, often not bothering to go out for meals and contenting himself with a glass of milk which became his chief article of food. He was discovered by friends in an utterly confused, disoriented, delirious condition. He was immediately placed in a hospital and upon further observation appeared to be in a hopelessly demented state. However, after several weeks of vigorous therapy, which included injections of liver extract, multiple vitamins supplemented by large doses of nicotinic acid and thiamin chloride, a carefully balanced diet, physical therapy, frequent visits from old friends, and the formulation of a plan for the future, he made a very substantial recovery. Some evidence of chronic brain tissue dysfunction remained, but this was not significantly greater than that noted by his acquaintances for some years. The patient lived for another five years, enjoying life, attending various meetings, and exhibiting his usual cantankerous personality.

2. A 78-year-old, highly intelligent widow had been for some years in the habit of spending the alternate six months of each year in the homes of a daughter and a son. Both families were well to do and the physical arrangements were about equally comfortable. However, the patient much preferred her daughter's home, being quite fond of her son-in-law. On the other hand, there was mutual antagonism between her and the daughter-in-law. Just prior to the date set for a move to her son's home, the patient had a mild, febrile illness diagnosed as influenza, which confined her to bed. Her appetite diminished to a point where she ate practically nothing; confusion, disorientation and a mild depression ensued. An examination revealed a definite nutritional deficiency, but in addition, even in spite of the confusion, it was possible to elicit a serious conflict related to the need to spend the next six months with her son and daughter-in-law. She was allowed to discuss her feelings in detail. The environment was manipulated to the extent of arranging to have her live at the home of her daughter and son-in-law permanently. The patient was given much supportive psychotherapy in addition to treatment directed toward correction of the nutritional disturbance. She ate her first hearty meal in weeks immediately following the first interview with the psychiatrist. Within a week recovery was complete.

3. A 78-year-old woman was observed in a moderately severe confusional state characterized by loss of memory for relationships between the members of her family and the details of their current activities. Formerly she had had no difficulty in remembering, for example, who had married whom. She was listless and moderately depressed. These symptoms came on following the death of her husband, with whom she had lived devotedly for many years. The confusion of persons seemed indicative of chronic brain syndrome. However, six months later all these symptoms had vanished, although the patient had had no treatment for them. The patient then placed people in her environment accurately and was no longer depressed.

4. A 73-year-old woman lived in Philadelphia with her sister who became ill. The sister's son, who also lived with them, found he could not care for both his mother and his aunt, so he rather hurriedly loaded the patient (his aunt) on a train with only half-completed arrangements for her care by friends in New Orleans. When she arrived in New Orleans, much fatigued by the journey, her friends, although surprised, welcomed her. However, having no room for her in their homes, they were obliged to find a room for her in a hotel. They noticed her confused and disoriented condition and sought medical assistance.

When examined, the patient showed a confusional state characterized by severe impairment of recent memory and disorientation for time and place. Although in New Orleans when examined, she believed herself at different times to be in Mobile and Philadelphia. She could not recall having made the journey from Philadelphia to New Orleans. She was somewhat aware of her disorientation and confusion, and perplexed by it. She was moderately depressed.

Immediately after the examination, arrangements were made for the transfer of the patient from the hotel to a boarding house run by an old and dear friend of the patient. Within a few hours she had improved markedly and seemed quite clear to her friend. When examined again the next day, her confusion had disappeared and she was well oriented. She recalled many of the events prior to the journey itself, and she was in good spirits.

5. A 78-year-old woman became somewhat irrational after the death of a beloved nephew who had been the last surviving member of her family and a frequent visitor to the patient in the old person's home where she resided. About four months after his death she had influenza and thereafter became much more confused.

When examined at this time, she was disoriented and markedly confused. Her memory was severely impaired and she showed poorly systematized delusions. The patient was treated with supplementary vitamins and Metrazol (grains 1½, four times daily). Within a few weeks the major symptoms of the psychosis cleared. The patient still showed confusion at times and still had some impairment of memory. However, she was usually active, alert, and interested in outside activities, as indicated by the considerable extent of her reading.

DISCUSSION

We recognize that in many elderly patients stress is greater, of longer duration, or less well adapted to, than in these 5 patients. Many patients fail to recover from a dementing psychosis in old age and continue psychotic until they die; yet the occurrence of cases such as those illustrated may remind the physician that some of these patients may be helped to recovery and further years of satisfactory life by attention to the remediable factors in the illness.

In several of the cases described here, more than one stressful factor was identified (*e.g.*, infection, nutritional deficiency, and threatened separation; fatigue and actual separation; and nutritional deficiency and retirement). In treating such patients the physician must carefully survey the whole physical and psychologic condition and the life situation of the patient, looking for causative factors.

Older persons are known to be more sensitive to stress than are younger adults. This fact is sometimes viewed pessimistically, but in practice it often transpires that just as old persons are disturbed by changes or stresses too slight to bother a younger person, so they may be helped by comparatively slight adjustments on the part of younger people. Case 2 illustrates this point.

Older persons are also usually considered beyond the reach of reconstructive psychotherapy. This is not always true; but even when it is, the patient may still benefit greatly from a psychotherapeutic relationship with the physician. This should include the opportunity to express feelings and grievances to another person who listens with respect and understanding. Such measures (as in Case 2) may bring notable relief and do much to reduce the tension accompanying a stressful situation.

SUMMARY

No clear relationship has been shown between anatomic changes in the brain and the occurrence of psychoses in elderly persons. Although it has been well established that the affective and paranoid psychoses of old age are amenable to electroshock therapy, an attitude of pessimism often dominates the approach to the treatment of the dementing psychoses. Since these psychoses are not predictably related to the extent of brain damage, at least two other factors must be considered: 1) The capacity of the patient to compensate for the loss of cerebral function. This may be more important than the loss of function itself, and is an expression of the adaptability developed by the patient in encountering previous life stresses. 2) Fluctuations in the compensating capacity of the patient, according to external circumstances. Physical and psychologic stresses may overwhelm the patient's compensatory ability, but the removal of these stresses or their diminution with time, may induce a return of adaptive capacity and recovery from the psychosis. Five cases of dementing psychoses of old age are described, in each of which there was recovery following cessation of the stress. Greater attention to the remediable causative factors in the dementing psychoses of old age may lead to more frequent recoveries.

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MULTIPLE MYELOMA

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Because of its many varied and unusual manifestations, multiple myeloma is one of the most interesting diseases confronting the physician engaged in the care of the aged. Although little has been added to our knowledge of the disorder in recent years, there appears to be an increase in the frequency of its diagnosis and, for this reason, a review of the subject seems worthwhile.

A description of this interesting and multifaceted disease first appeared in the medical literature in 1845 when Sir James Watson noted in the urine of one of his patients a substance which solidified on cooling. Henry Bence Jones (1), to whom samples of this urine were sent, found that this substance (thereafter called Bence Jones protein) precipitated when heated, cleared when boiled and solidified when cooled. He also reported that at necropsy "the bony structure of the ribs was cut with the greatest ease, and that the bodies of the vertebra were capable of being sliced off with a knife," and concluded that the substance in the urine was "an oxide of albumin" which might be present in other cases of "mollities ossium." The following year J. Dalrymple (2) first reported on the gross and microscopic appearance of the bone and described the replacement of bone by nucleated cells. It was he who first suspected the malignant nature of the disease.

The name multiple myeloma was given to the condition by von Rustizky (3) in 1893. In 1899 Kahler (4) enumerated its cardinal symptoms: bone pain, deformity and abnormal fragility of the bones, cachexia and the presence in the urine of Bence Jones protein. Ten years later the interrelationship of hyperproteinemia and multiple tumors of bone was first noted in a report by Ellinger (5). The identity of the tumor cells with plasma cells was pointed out by Wright (6) in 1900.

CLINICAL DATA

Age incidence

This report is based on the findings in 31 cases seen in the Guthrie Clinic-Robert Packer Hospital since 1947.

Although still a rare disease, recent years have seen an upswing in its reported incidence, undoubtedly due to more expert hematologic and pathologic examinations plus the fact that more people are living longer and it is in the older age group that the disease is most common. Table 1 shows the age incidence in the group of 31 cases studied here.

Sex incidence

Cases have been reported from all parts of the world and all races appear susceptible. It is said to occur twice as frequently in males as in females. In our

TABLE 1

Age	No. of Patients
40–49	3
50–59	4
60–69	14
70–79	8
80-up	2

Youngest, 41; oldest, 84; average, 66.

series, 19 patients were males and 12 females. All were white but this is probably not significant, in that the great majority of our admissions are drawn from a predominantly white community.

Symptomatology

The symptomatology of the disease is protean. Pain is the most frequent presenting complaint, and it is commonly due to a pathologic fracture. Moderate weight loss is a usual early finding and in the later stages it may assume cachectic proportions. This is not at all surprising in view of the pronounced proteinuria noted in some cases.

About 50 per cent of all cases have a low-grade remittent fever, and terminally the temperature may reach 106° to 107°F. The etiology of this hyperpyrexia is obscure.

Although there is usually no abnormality in prothrombin time or bleeding and clotting time, bleeding tendencies are rather common. Epistaxis, ecchymosis, bleeding lips and gums, petechiae, hematemesis or melena are noted in 30 to 40 per cent of the cases, perhaps due to the thrombocytopenia which is often present.

Neurologic disorders are not uncommon and often are the presenting symptoms. Usually they are due to pathologic fractures of vertebrae. Radiculitis, intercostal neuralgia and paraplegia are frequently seen.

Hepatomegaly and splenomegaly are fairly common, the former occurring about three times as frequently as the latter. Various explanations offered for the enlargement of the liver and spleen are: 1) compensation for loss of bone marrow, 2) toxemia, and 3) metastases. It is rare that the lymph nodes are reported as hyperplastic.

Palpable tumors are often present and may be the presenting complaint. Generally these are non-tender, and pulsatile and vary in diameter from 1 cm. to 15 cm. Their chief sites of origin are the ribs and sternum; the skull, femur, pelvis, vertebra and humerus are less frequently involved in the order named. Characteristically, the tumors are multiple, but it is thought that the growth usually arises as a single form which often assumes considerable dimension before multiple tumors appear. The possibility of multiple origin cannot be excluded, however.

A review of the symptomatology and findings in our 31 cases shows that in 25 the presenting symptom was pain. One patient reported with a right facial

paralysis, 1 with urinary retention, 1 with numbness of the hands, 2 with nosebleed and 1 with hematemesis. In 9 the pain was sudden in onset and was probably the result of a pathologic fracture. Weight loss of moderate to severe degree was present in 23 cases, and 15 patients had a low-grade fever. Bleeding tendencies were noted in 14 patients, 8 having epistaxis, 2 hematemesis and 4 tarry stools. Only 5 had hepatomegaly and 1, splenomegaly. Of those with neurologic disorders, 4 had paraplegia; 1, right facial paralysis; 1, branchial plexus involvement; 1, intercostal neuralgia; and 6, sciatica. In 5 cases there were palpable tumors—in the ribs in each instance.

Laboratory findings

In several reported series of cases the incidence of Bence Jones protein varies from 8 per cent to 87 per cent, with an average slightly over 50 per cent. During the early course of the disease its appearance may be intermittent. Electrophoretic studies have shown that this substance is not a single entity but a group of proteins with closely related properties. In general, it is said to be found in cases in which the protein content of the blood is normal or even low, but we were unable to verify this in our series. The urine was examined in 29 of our 31 patients and Bence Jones protein was found in 8. In these 8 patients, the serum protein level was elevated in 6, normal in 1 and low in 1. In 12 patients with negative urinary findings the blood protein levels were normal or low. No correlation was noted between the globulin or albumin fraction and the occurrence of Bence Jones protein.

One of the commonest laboratory findings is an increased concentration of total serum protein. This is usually seen with a reversal of the A/G ratio, the albumin fraction being reduced and the globulin fraction being elevated. Because of the decreased albumin fraction, there may be a hyperglobulinemia without a hyperproteinemia. Serum protein levels were determined in all but 3 of our cases and a total protein concentration above 8.0 grams per cent was found in 13 cases. In 21 cases the A/G ratio was greater than 1/1. In 11 cases there was hypoalbuminemia and in 24 cases there was hyperglobulinemia.

Another great diagnostic aid is a study of the peripheral blood. Most patients have an anemia, usually of the normocytic, normochronic type. A macrocytic type is not unusual, however. In 29 of our 31 cases the hemoglobin was below 12 grams per cent, and in 11 cases it was 9 grams or lower. The highest level was 14.5 grams, the lowest 5.5 grams, and the average 9.6 grams. A computation of the mean corpuscular volume, hemoglobin, and hemoglobin concentration was impossible, since the hematocrit was seldom determined, but the color index was usually in the range of 0.9 to 1.1.

Often it is hard to count the red cells because of clumping due to autohemagglutination. Other manifestations of this same phenomenon are the difficulties in typing blood, excessive rouleaux formation, and the extremely rapid sedimentation rate which is characteristic of the disease. The sedimentation rate (Cutler method) was determined in only 11 cases, but was increased in all; it was over 30 in 10 patients with a marked first-zone curve.

In 8 of our cases plasma cells were noted in the peripheral blood smear.

Perhaps the greatest diagnostic tool is hematologic study of the bone marrow. By the time the signs and symptoms of the disease are present the sternal marrow is usually well infiltrated and its study at this point usually enables the hematologist to confirm the diagnosis. The outstanding feature is the presence of the so-called "myeloma cells." The marrow is generally rather cellular and these cells vary in number from case to case. The different morphologic pictures which they present are probably due to differences in their ages. These cells ranges from the malignant type (fairly large, with dark blue nongranular cytoplasm, the round or oval nucleus occupying three fourths to four fifths of the cell and containing three or four nucleoli, and often mitotic figures) to the typical plasma cell (much smaller than the malignant type, and having dark blue cytoplasm and an eccentrically placed nucleus filling less than half the cell). Wallgren (7) and others have concluded that these different forms of cells merely represent stages of differentiation of a common cell from which they are all derived. Other investigators identify the myeloma cell as the reticulum cell of lymphoid tissue and regard it as a primitive mesoblastic cell, capable of differentiation according to local conditions. It may give rise to the simple reticulum-cell sarcoma of the lymph nodes and the spleen; and in the marrow it may be the source, not only of reticulum cells and endothelioma of bones, but also of plasma cells, myelocytes and erythroblasts.

Attempts have been made to show that the production of globulin is a function of the plasma cells. If this were true, there should be a correlation between the percentage of marrow plasma cells and the serum globulin level, but no such relationship was apparent in this study.

Practically all cases with urinary Bence Jones protein have renal insufficiency. Although multiple theories have been advanced to account for this phenomenon, the pathogenesis remains unknown. It would seem, however, that once Bence Jones protein appears, renal insufficiency has usually begun and the course of kidney failure is progressive. Azotemia gradually develops and many patients die of uremia. Six of our 8 patients with Bence Jones protein had renal insufficiency. It is of interest, however, that hypertension rarely accompanies this form of "nephritis."

Hypercalcemia is a common finding, as is an increase in alkaline phosphatase but the blood phosphorus level is usually normal. Table 2 summarizes these findings in our cases.

Roentgenographic evidence of bone disease is said to be present in about 90 per cent of all cases. The characteristic change is described as a typical "punched out" area with sharply demarcated margins and no surrounding reactive bone.

TABLE 2

Blood Level	No. of Cases	Normal	High	Low
Calcium	18	5	11	2
Phosphorus	17	13	4	0
Alkaline phosphatase	22	13	9	0

TABLE 3

Frequency and Location of Bone Lesions as Demonstrated by X-Ray

Bones Involved	No. of Cases	Per Cent	Pathologic Facture
Skull	12	39	
Vertebrae	10	32	15
Ribs	10	32	5
Humerus	7	23	
Femur	7	23	
Pelvis	6	19	
Scapula	2	7	
Mandible	1	3	
Generalized osteoporosis	6	19	
Osteoporosis plus lytic lesions	11	35	

Such lesions were found in 23 of the 29 patients in our series who had roentgenographic examinations. Frequently, however, these lesions were difficult to distinguish from carcinomatous metastases. The bones most frequently involved are the ribs, sternum, vertebrae, calvarium, pelvis and long bones; the radius, ulna, tibia, fibula, and the bones of the hands and feet are seldom affected. Just as common as the lytic lesions, however, is a widespread osteoporosis. Such a picture may be the only x-ray finding and this was true in 6 of our cases, as is shown in Table 3.

Amyloidosis as a complication of multiple myeloma is reported (8), but no cases were encountered in our series.

Differential diagnosis

Because of the multiplicity of factors in the differential diagnosis, the easiest approach is perhaps to group these factors under diseases of bone, anemias, renal disease and certain febrile diseases. The diseases of bone can usually be differentiated by x-ray studies and determinations of the levels of serum calcium, phosphorus, and alkaline and acid phosphatase. Bone marrow studies serve to differentiate the anemias. The presence of Bence Jones protein in the urine, the absence of x-ray evidence of renal pathology, and the low incidence of hypertension with renal failure due to multiple myeloma, are helpful in the consideration of renal disease. It is important to remember that fever is frequently seen in multiple myeloma. Thus, when unexplained temperature elevations are observed, this disease should be kept in mind.

Course

Although remissions are not infrequently reported, the usual course of the disease is progressive from the very onset of symptoms. Considerable individual variation is seen, however. Some patients die within a few months, and others live five or six years. The average patient will not survive longer than two years.

In only 15 of our cases was the survival period known and this averaged

thirteen months, the shortest being one month and the longest forty-four months. Survival, in general, seemed to bear little relationship to the type of treatment.

Treatment

Six patients were treated with urethane alone and in 2 of these the survival period was not known; however, neither showed any subjective or objective improvement during the period we were able to follow them. Another of the 6 lived two months after therapy was started and had considerable nausea and a leukopenia. Two lived six months and nine months, respectively, without improvement. The sixth urethane patient died a few days after the institution of therapy. Stilbamidine, alone, was given to one patient. There was no relief, and death ensued in one month.

In our hands, irradiation gave the best palliative results. Three patients were given stilbamidine and x-ray irradiation. Two obtained relief of pain and lived thirty months and twenty-four months, respectively. Urethane and palliative irradiation was used in 1 patient with good initial results, but he soon became worse and died in nine months. Seven were given palliative x-ray therapy only. Six of these had varying degrees of relief from pain, but the remaining 2 had no relief.

SUMMARY

The subject of multiple myeloma has been reviewed and the findings in 31 cases seen at the Robert Packer Hospital and Guthrie Clinic have been presented. The disease is uniformly malignant and is usually rapidly fatal. There are many unusual and unexplained manifestations. Bone marrow studies appear to be the best diagnostic instrument to date. Although no curative form of therapy has appeared, irradiation affords relief of pain in many cases.

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PALLIATIVE SURGERY IN CANCER OF THE RECTUM AND COLON

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One of the recurring problems presented to physicians is that of how to achieve palliation most satisfactorily in the patient with incurable cancer of the colon and rectum. It is difficult to make precise statements in this regard, as the interpretation of what constitutes palliation differs widely, not only with the patient and his family but with the family physician and surgeon. A procedure which may be considered worthwhile by the surgeon may be considered useless or worse by the patient or his family, and one which may be considered meddlesome by the family physician may be gratefully received by the patient. Until more precise standards are defined the usually accepted evaluation in terms of longevity and symptomatic relief will have to serve as a basis for our decisions.

Surgical removal of the primary neoplasm is being performed with increasing frequency in the hope of achieving palliation for incurable cancer of the colon and rectum as well as for cancer in other organ systems (1). Whether this can effect the desired purpose more satisfactorily than other means (for example radiation therapy) will determine our handling of individual patients. Until research provides better agents, surgery and radiation therapy remain the most generally applicable methods for bringing some measure of relief to these patients.

CLINICAL MATERIAL

The purpose of this article is to present data concerning relief of symptoms and prolongation of life in a group of patients with incurable cancer of the colon and rectum treated palliatively by surgery. Patients who had had previous treatment for the primary neoplasm and came in with recurrent disease were not included. This series consisted of cases considered incurable when first seen for definitive treatment, or found to be so at the time of exploration.

There were 57 patients on whom palliative operations were performed by members of the Rectum and Colon Service at Memorial Center between 1946 and 1952. In all of these, irremovable cancer was left following resection, either locally or distant.

A summary of the symptomatic relief obtained in these patients, according to the site of the primary neoplasm and the residual cancer, is shown in Table 1. By way of explanation, "Disease left locally" indicates that in this group there were no other signs of distant metastases or spread. For example in the group listed under "Rectum," tumor was left in the pelvis only. In the other

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TABLE 1

Symptomatic Relief Following Palliative Resection

Site of Primary Neoplasm		No. of Cases	Relief Obtained		Duration (months)
			Degree	No. of Cases	
Rectum	*Disease left locally*	8	None	3	
			Minimal	2	
			Moderate	1	11
			Complete	2	4
Left colon		1	Moderate	1	6
Rectum	*Peritoneal metastases*	5	Postop. death	1	
			Minimal	1	
			Complete	3	15–23
Left colon		1	Complete	1	6
Right colon		3	None	1	
			Complete	2	4–6
Rectum	*Liver metastases*	23	No evaluation	3	
			Postop. death	1	
			Minimal	4	
			Complete	15	6–72
Left colon		5	Minimal	1	
			Complete	4	5–19
Rectum	*Multiple sites*	7	Moderate	2	9
			Complete	5	6–12
Left colon		3	Minimal	2	1
			Complete	1	10
Right colon		1	Complete	1	14

TABLE 2

Survival Rates: Palliative Resection vs. No Resection

Site of Primary Neoplasm		No. of Cases		Survival (months)			
				From onset of symptoms		From time of admission or treatment	
		Not resected	Palliative resection	Not resected	Palliative resection	Not resected	Palliative resection
Rectum	*Disease left locally*	27	8	22	17	12	9
Left colon		1	1	18	14	5	8
Rectum	*Peritoneal metastases*	0	5		20		15
Left colon		2	1	7		3	23
Right colon		2	3	12	25	9	10
Rectum	*Liver metastases*	13	20	15	28	6	17
Left colon		1	2	13	26	3	21
Rectum	*Pulmonary metastases*	4	3*	24	27	10	13
Rectum	*Multiple sites*	27	7	19	29	8	17
Left colon		0	3		16		8
Right colon		3	1	30	14	12	11

* All showed liver metastases at the time of exploration.

categories the only residual disease was at the site listed. The degree of relief obtained was determined according to the patient's statement as to freedom from pain and his ability to be ambulatory.

To evaluate as accurately as possible the influence of liver metastases we included only those cases that were proved histologically or in which the operative description left no doubt that gross metastases existed. Thus we excluded 33 of 61 patients classified by the surgeon as having had a palliative operation, because the description of the operative findings left some doubt as to the actual presence of metastases. We also excluded the patients who had resections of an apparently solitary liver metastasis.

The attempt to determine whether or not prolongation of life had been achieved was made by comparing these patients with a group of patients in similar categories treated prior to 1946 who did not have resection of the primary neoplasm. This comparison is shown in Table 2.

RESULTS AND DISCUSSION

Statements concerning palliation are unsatisfactory because of the lack of precise definition of terms. Evaluation of the procedure in terms of relief of symptoms is subjective. Data concerning prolongation of life are only comparative and subject to the criticism that it is probably impossible to obtain two strictly comparable series of patients with cancer, differing only in the method of treatment.

With these limitations in mind, the results as shown in Table 1 indicate that: 1) very little relief of symptoms was obtained in those in whom palliative resection was incomplete, leaving residual tumor at the site of the primary neoplasm; 2) symptomatic relief, classed as complete and averaging fourteen months, was obtained in most of the patients considered incurable because of distant metastases; and 3) complete symptomatic relief for an average duration of eighteen months was obtained in 15 of 20 patients with liver metastases only.

Table 2 indicates that: 1) not only was no prolongation of life obtained, but an apparent shortening of life resulted when incomplete resections were performed, leaving tumor locally at the site of the original neoplasm; 2) no substantial prolongation of life was noted among those who had palliative resections of the primary lesion in the presence of distant metastases other than liver metastases; and 3) an apparent prolongation of life of about one year was obtained in those patients who had palliative resections in the presence of liver metastases.

Much remains to be done in determining how to handle the patients who present themselves with incurable cancer of the colon and rectum. At the present time it seems that surgical removal results in relief of symptoms, and often prolongation of life, if it is not necessary to leave residual neoplasm at the site of the primary tumor.

SUMMARY

1. Fifty-seven patients undergoing resections of primary tumors in the presence of known residual cancer were studied.

2. Symptomatic relief of worthwhile duration was obtained in patients having palliative resections in the presence of distant metastases.

3. Following resection of the primary neoplasm, prolongation of life for about twelve months was obtained in patients with cancer of the rectum and liver metastases.

4. Neither satisfactory symptomatic relief nor prolongation of life was obtained by palliative resection in patients in whom residual tumor was left at the site of the primary neoplasm.

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Abstracts of Current Literature

EMOTIONAL PROBLEMS OF THE MIDDLE-AGED MALE.

Billig, O., and Adams, R. *Psychiat. Quart.* **28:** 442 (July) 1954; through *Digest. Neurol. & Psych.*, November 1954, p. 513.

Two vulnerable periods can be expected in the adult male who had not resolved his Oedipal conflict: 1) at the birth of a child, particularly of the first male child, and 2) at middle age, when he fears that his real or symbolic son (*e.g.*, younger co-worker) has grown sufficiently powerful to displace him. His own unresolved Oedipal conflicts make him vulnerable in his role as elder, and his rivalry with the younger man is of basic dynamic significance. The underlying conflicts may be reactivated, resulting in anxiety or in depressive reactions and, although they do not always reach proportions of clinical magnitude, only if such conflicts are resolved can the middle-aged man live and work with a younger man without needing defenses against potential threats. Middle-aged depressions have been more frequently recognized in "successful" men. Certain cultural factors can be important in reinforcing existing conflicts. In Western culture the successful man of middle age has reached an important period in his life. To be successful he has had to struggle and to compete and the competition is based on "conditioned" love; lack of success may mean loss of love. The dynamic struggle between rivals has been most often observed from the point of view of the one struggling for success and, seemingly, the older man's fear of his younger rival has not been sufficiently emphasized. Among men of low-competitive social groups, where love and approval are not conditioned on success, existing Oedipal conflicts tend to be expressed in conversion or anxiety reactions. A study of about 150 patients from a culturally restricted environment in isolated mountain areas revealed a high incidence of emotional illnesses in men between the ages of 35 and 55 years. These illnesses were primarily anxiety and conversion reactions, although psychosomatic problems were sometimes prominent. Unresolved Oedipal feelings in connection with a strict, threatening father were a major feature of the psychodynamics. The writers found treatment difficult in all of their cases. Depressed patients showed considerable resistance to therapy. Courses of 12 to 15 electroshock treatments produced only temporary results and further electroshock therapy produced no additional benefits. In some cases, marked personality disorganization occurred and disappeared spontaneously within two to four weeks when this therapy was discontinued. Even in the absence of cultural limitations, giving insight into the simplest dynamic mechanisms meant intensive psychotherapy over a period of from one to four years.

TEMPORAL ARTERITIS.

Chipman, C. D. *Canad. M.A.J.* **71:** 382 (Oct.) 1954.

Temporal arteritis is a nonspecific, nonsuppurative inflammation of arteries which is most obvious in the superficial temporal vessels and which a review of published cases shows to be distinct from other forms of arteritis. One case is presented. Temporal arteritis usually occurs between the ages of 55 and 80 years. The onset is insidious, with vague systemic symptoms such as anorexia, weight loss, malaise and fever. Disturbances of vision are frequently found and sometimes blindness occurs. Beading and tenderness of the temporal artery and its branches become apparent, as well as erythema and edema of overlying skin. Other findings include moderate anemia, polymorphonuclear leukocytosis without eosinophilia, and an elevated sedimentation rate. The course is gradual subsidence and the prognosis is generally good, although the natural history of the disease has not been estab-

lished. Histologically the picture is of panarteritis, and all layers of the vessel are affected. Excision of a section of the temporal artery may relieve local pain. Injection of the vessel locally with 1 per cent procaine hydrochloride solution and blocking of the stellate ganglion have been tried with some success. The effect of antihistamines has been difficult to evaluate because of sedative and analgesic properties. There was no apparent benefit from the administration of tetracycline for one week in the case reported. Recently corticotropin and cortisone have brought about dramatic relief and a rapid decrease in temperature but not a consistent reduction in sedimentation rate. These drugs probably suppress the inflammatory process until a spontaneous remission occurs.

THE VALUE OF RAUWOLFIA SERPENTINA IN THE HYPERTENSIVE PATIENT.

Finnerty, F. A., Jr. *Am. J. Med.* **17:** 629 (Nov.) 1954.

The present status of studies on 89 hypertensive patients, treated with Rauwolfia alone or in combination with other more potent hypotensive agents, permits the following conclusions: When used alone, Rauwiloid proved to be definitely superior to mild barbiturate sedation for the reduction of blood pressure and for the relief of anxiety in patients with normal eyegrounds or with Grade I hypertensive retinopathy. When added to Veriloid, Rauwiloid frequently made it possible to decrease the dose of Veriloid by one-third or more, thus reducing significantly the incidence of nausea and vomiting, and also enhancing the hypotensive effect. When added to hexamethonium and Apresoline in severe hypertension, Rauwiloid made possible a reduction in the hexamethonium dosage by one-third or more in all but 5 cases and eliminated the need for Apresoline entirely in all but 4 cases. The blood pressure remained the same or improved. The side effects induced by hexamethonium and Apresoline were either greatly reduced or eliminated altogether. (From author's summary and conclusions.)

THE VALUE OF THE ROUTINE CHEST X-RAY FILM IN DETECTING DIAPHRAGMATIC HERNIA; A REPORT OF 53 CASES.

Froman, A. *Dis. Chest* **26:** 457 (Oct.) 1954.

The routine chest x-ray examination is useful in the diagnosis of diaphragmatic hernia. The finding of an enlarged square-shaped or globular cardiac silhouette indicating a large air pocket, with or without a horizontal fluid level, is virtually diagnostic of hiatal hernia. Small faint air bubbles or streaks of air along the right or left borders of the heart are also suggestive of hiatal hernia. The ovoid elongated homogeneous shadow that causes variations in density within the cardiac silhouette is usually due to a hiatal hernia. Any massive shadow within the lung field, continuous with the diaphragmatic outline and obscuring it, or any shadow in which continuity is incomplete above the diaphragm, is suspicious of diaphragmatic hernia of the Morgagni type or of traumatic origin. X-ray examination by means of the barium meal and/or barium enema is obligatory for final confirmation of the suspected condition. Diagnostic pneumoperitoneum may be employed in cases in which herniation of the omentum or part of the liver is suspected. (From author's conclusions.)

PARALYTIC ILEUS FOLLOWING USE OF BANTHINE DURING GASTROINTESTINAL BLEEDING.

Gunn, C. G., Jr., and Allen, M. S. *New England J. Med.* **251:** 705 (Oct. 21) 1954.

Five cases of upper gastrointestinal hemorrhage in which paralytic ileus during Banthine therapy developed are reported. Other causal factors were apparently absent. It is believed that gastrointestinal hemorrhage constitutes a contraindication to Banthine therapy. A diagnosis of intestinal obstruction indicating surgery should be made with caution in patients with gastrointestinal bleeding under treatment with Banthine. (Authors' summary and conclusions.)

JAUNDICE OCCURRING DURING METHYLTESTOSTERONE THERAPY. CASE REPORT AND REVIEW.

Henry, O., and Cayer, D. *North Carolina M. J.* **15:** 499 (Oct.) 1954.

A survey of reported cases of jaundice occurring during methyltestosterone therapy shows that 11 occurred in males and 3 in females. Ages ranged between 15 and 74 years and averaged 45 years. The duration of treatment varied from 8 to 230 days, and the dosage from 10 to 100 mg. per day. In the majority of cases the jaundice was severe and prolonged, persisting from two weeks to five months. In a few patients methyltestosterone was readministered, after the jaundice subsided, without recurrence. The disorder appears to be self-limited and without obvious sequelae. Its pathogenesis is poorly understood. Liver biopsies indicate that fatty infiltration, if it occurs, is not pronounced; therefore, a choline deficiency seems unlikely. The consistent histologic finding of plugging of the small bile canaliculi suggests the possibility that the changes observed are due to an altered viscosity of the bile. The histologic appearance seems sufficiently distinctive to rule out infectious or inflammatory hepatitis. The cases of jaundice following methyltestosterone therapy show sufficient similarity of unusual biochemical and pathologic findings to justify withholding surgical exploration in such patients with otherwise negative findings. However, there still is not enough evidence to show that methyltestosterone is the sole cause of these unusual instances of jaundice. Jaundice developed in the patient reported after one year, at a dosage level of 10 to 30 mg. daily.

CHLORPROMAZINE IN PATIENTS WITH NAUSEA AND VOMITING DUE TO ADVANCED CANCER.

Homburger, F., and Smithy, G. *New England J. Med.* **251:** 820 (Nov. 11) 1954.

Chlorpromazine produced prompt relief of nausea and vomiting of patients with advanced incurable cancer when given orally or intramuscularly. Emesis was controlled for as long as four months. The only side effects observed in 20 patients studied for this period were occasional drowsiness and dryness of the mouth. (Authors' summary.)

A PROCEDURE TO AID IN THE EVALUATION OF PERIPHERAL CIRCULATORY FUNCTION IN OLDER SUBJECTS.

Landowne, M.; Silverstone, F., and Silver, H. M. (Proc., 8th Ann. Meet., Am. Soc. Study of Arteriosclerosis.) *Circulation* **10:** 584 (Oct.) 1954.

Skin-temperature responses to the indirect vasodilatation induced by heating the trunk were studied in order to obtain normal data as the basis for clinical evaluation of the peripheral circulation, particularly in the older individual. The average maximal toe temperature among 78 males aged 26 to 92 years (mean 58) was 30.7 ± 3.6° C. Among them, 12 were graded functionally as Class II and the remainder as Class I. A higher-than-mean toe temperature was attained by 34 of the 38 patients who were below the mean age. Two of these were Class II. Seventeen older subjects behaved similarly. In the remaining 23 older subjects, toe temperature did not exceed 30° C. Among the 10 older subjects in Class II, only 1 showed a rise over 30° C. Toe temperatures in 8 subjects with peripheral vascular disorders failed to reach 30° and only 2 exceeded 25° C. This procedure, interpreted cautiously, is useful in screening for possible functional impairment in the absence of clinical history, symptoms, or signs of a peripheral circulatory disorder.

EMBOLECTOMY FROM ARTERIES OF THE LOWER LIMBS. AN ANALYSIS OF FIFTEEN CASES.

Leonard, F. C. *New England J. Med.* **251:** 595 (Oct. 7) 1954.

Nine among 15 embolectomies during a four-year period were successful. No patient died as a result of the operation and no limbs were lost in the last 7 embolectomies. Eight of the operations and 5 of the successful ones were performed in elderly arteriosclerotic

patients, 4 of them between the ages of 71 and 80 years. The procedure should not be denied a patient because he is old and arteriosclerotic. There is apparently a trend away from the classic rheumatic heart as a source of emboli. Retrograde blood flow, which is of prognostic significance, was present or capable of establishment in all cases seen early and in all 9 successes. Half of the 6 deaths in the series were from pulmonary embolism despite adequate anticoagulation therapy. Therefore, consideration of femoral-vein interruption with lower-limb embolectomy is warranted. Embolectomy is the treatment of choice at the aortic, iliac and femoral bifurcations. The diagnosis can usually be made by manual and visual examination and from the history of sudden pain followed by paresthesias, coldness and early paralysis of the affected leg. No pulse is felt beyond the involved bifurcation but a vigorous pulse comes down to it. Embolectomy should be performed within eight hours whenever possible, but should not be abandoned once this arbitrary limit has been exceeded. Most lower-limb embolectomies can be performed with novocaine alone. Occasional direct aortic and iliac embolectomy requiring general anesthesia should be reserved for the air-risk patient seen before irreversible shock appears.

THE DIAGNOSIS OF DEPRESSION.

Mayer-Gross, W. *Brit. M. J.* **2:** 948 (Oct. 23) 1954.

Depression as a psychiatric symptom is probably the most common complaint of psychiatric patients today. During the last twenty years it has become more frequent as the presenting symptom of neurosis, and this has aggravated the diagnostic problem. For rational therapy the reactive, neurotic form of depression has to be differentiated from the endogenous depression with little or no environmental etiology. Physical treatment methods, especially convulsive therapy, can rapidly relieve depression in many patients. This treatment has to be based on an etiological diagnosis and combined with other measures adapted to the special circumstances of the case. Many patients suffering from periodic indigestion, "bilious attacks," and other intestinal complaints are, in fact, suffering from recurrent depression, as are some cases diagnosed as "hysteria." The differential diagnosis of depression in the elderly, from senile dementia and arteriosclerosis is of great value in the treatment and disposal of geriatric patients. (Author's summary.)

THE NORMAL POST-MENOPAUSAL ENDOMETRIUM.

McBride, J. M. *J. Obst. & Gynaec., Brit. Emp.* **61:** 691 (Oct.) 1954.

A study was made of the results of curettage in 1,521 postmenopausal patients who had not suffered from bleeding since the cessation of menstruation. Histologic findings are described. Simple atrophy was found in 31.5 per cent of the 206 cases in which endometrium was obtained for microscopic examination. The incidence of active hyperplasia was 12.6 per cent, but reasons were adduced for the belief that this figure was artificially high. Most cases occurred in the early postmenopausal years. An inactive, cystic gland pattern was noted in 42.7 per cent of cases; in the majority of instances it was in polyp formation. Investigation of uteri obtained at autopsy confirmed that this gland pattern was of common occurrence and suggested a mechanical explanation. Histologic and clinical findings did not provide any evidence that this gland pattern was related to endometrial hyperplasia or to excessive estrogenic activity. The fact that active hyperplasia and endometrial polypi of cystic gland pattern occur in women past the menopause who have not suffered from bleeding must be taken into consideration in the interpretation of the endometrial pattern observed in cases of postmenopausal bleeding and in association with endometrial carcinoma (From author's summary.)

LIVER FUNCTION AND HYPERTENSION. BLOOD PRESSURE AND HEART WEIGHT IN CHRONIC HEPATITIS.

Raaschou, F. *Circulation* **10:** 511 (Oct.) 1954.

The incidence of arterial hypertension in an autopsy series of 102 women who died of chronic hepatitis (subchronic yellow atrophy of the liver) was compared with that in a

control autopsy series of patients without liver disease. The study demonstrated, by means of the incidence of cerebral hemorrhage and of hypertrophy of the heart and the incidence and degree of arterial hypertension, that arterial hypertension was less frequent in the group with severe hepatic disease. The hypothesis is presented that severely impaired liver function may prevent the development of, or can eliminate already existing arterial hypertension.

THE CONTROL OF MALIGNANT EFFUSIONS WITH RADIOACTIVE GOLD.

Schick, A., and Bloor, R. J. *New York State J. Med.* **54:** 2979 (Nov. 1) 1954.

Radioactive gold is a valuable therapeutic tool for the control of serous effusion due to malignant implants. It should be reserved for patients in reasonably good clinical condition, whose chief difficulty is a rapidly forming malignant effusion. If the first application of gold elicits a clinical response which is incomplete, the second dose may stop fluid production completely. The immediate side-effects following gold administration are slight and easily controlled. In most patients gold will evoke a fibrous response of the serous surfaces. There is some evidence that this fibrous response at least partially determines the therapeutic effect of gold. Criteria are given for the selection of patients to receive radioactive gold. (From authors' conclusion.)

FIRST INTERIM REPORT ON THE EFFECTS OF ESTROGEN THERAPY IN MALES UNDER 50 YEARS OF AGE WITH A PREVIOUS SINGLE MYOCARDIAL INFARCTION.

Stamler, J.; Pick, R., and Katz, L. N. (Proc., 8th Ann. Meet., Am. Soc. Study of Arteriosclerosis.) *Circulation* **10:** 587 (Oct.) 1954.

One hundred patients with coronary atherosclerosis were subjects of a long-term study of the possible efficacy of estrogens in the disease. Of these, 69 were males under 50 years of age, who had recently had a single proved myocardial infarct. Divided into two almost identical groups as to mean age, weight, duration of treatment, plasma cholesterol level, and pretreatment plasma total cholesterol-lipid phosphorus ratio, they received estrogen or placebo. Oral estrogen dosages were increased stepwise from 1.25 or 2.5 mg. of conjugated estrogenic substances to 4.0 to 10.0 mg. Only rarely did the side effects—gynecomastia, loss of libido, impotence—result in discontinuation of therapy. Dosages of 1.25 to 4.0 mg. had no effect on plasma total cholesterol levels. Higher dosages tended moderately to lower the plasma C/P ratio. As of June 30, 1954, a second proved myocardial infarction had occurred in 6 of the 26 patients in the placebo group treated for two months or longer. Three were fatal. No second myocardial infarction occurred in the 39 patients under estrogen therapy for a similar length of time. Conclusions cannot yet be drawn. The study is continuing.

POSTMENOPAUSAL ENDOMETRIAL TUBERCULOSIS. AN UNUSUAL CASE WITH A REVIEW OF PREVIOUS REPORTS.

Towers, R. P. *J. Obst. & Gynaec., Brit. Emp.* **61:** 657 (Oct.) 1954.

A case of tuberculous pyometra in a woman 73 years of age is presented, and the literature on postmenopausal endometrial tuberculosis briefly reviewed. This is a relatively uncommon condition. Approximately half of the reported cases occurred during the years immediately after the menopause. The available evidence indicates that the disease begins sometime after the climacteric and probably is not present in earlier life. The pathology of the condition is discussed. It is considered that postmenopausal hematogenous spread to the uterus through the tubes with progression of the disease to gross caseous ulceration is the usual sequence of events. Vaginal bleeding and leucorrhea are the most frequent signs. Pain (hypogastric in distribution) and discomfort in the perineum may be present. As there is no need to conserve the uterus and little likelihood of antibiotics penetrating the lesions, total hysterectomy with bilateral salpingo-oöphorectomy is the treatment of choice.

COMBINED TREATMENT OF RHEUMATOID ARTHRITIS WITH SOLGANAL AND CORTISONE.

Warter, P. J. *Clin. Med.* **61:** 757 (Oct.) 1954.

Combined aurothioglucose and cortisone in the treatment of 30 patients with rheumatoid arthritis aided all except 2, and achieved results superior to those with either drug alone. Sixteen of 18 patients, whose condition had become static and who were without a satisfactory remission during gold therapy, derived additional benefit when cortisone therapy was begun in a dosage of 100 mg. daily and aurothioglucose was continued in a dosage of 25 mg. per week parenterally. The cortisone dosage could be reduced to 75 and 50 mg. daily in 3 and 11 patients, respectively, without diminution in their response. It could be discontinued after fourteen weeks in 2 patients. Maintained on a biweekly dose of Solganal, no reactivation of the rheumatoid process occurred in these patients during the subsequent six months. Six patients, 4 of whom had previously received ACTH, were started on aurothioglucose and cortisone simultaneously. The cortisone dosage could be reduced from 100 to 50 mg. the second week, and later discontinued. Improvement that was moderate in 1, excellent in 3, and dramatic in 2 occurred during this therapy and could be maintained with biweekly administration of aurothioglucose. The combined use of aurothioglucose and cortisone in 6 patients in whom remissions were no longer maintained under gold therapy resulted in their return to work an average of thirty-five days earlier than when gold alone was used. There were no toxic symptoms or findings during the period of treatment with the drugs in combination.

PREVENTION OF SYSTEMIC ARTERIAL EMBOLISM IN CHRONIC RHEUMATIC HEART DISEASE BY MEANS OF PROTRACTED ANTICOAGULANT THERAPY.

Wood, J. C., and Conn, H. L., Jr. *Circulation* **10:** 517 (Oct.) 1954.

Seven patients with mitral stenosis and chronic auricular fibrillation complicated by one or more systemic embolic episodes received Dicumarol for periods of twenty to forty-eight months. The drug was begun immediately after an embolic episode in 6 patients. Each received heparin until adequate prolongation of the prothrombin time was achieved with Dicumarol. The seventh patient received the drug one year after a cerebral embolism. The average daily maintenance dose varied between 100 and 175 mg. in 1 patient, 50 and 75 mg. in 4, and 25 and 50 mg. in 2. Prothrombin levels between 20 and 35 per cent were maintained in most of the patients. Only one recognized embolism occurred during therapy. Dicumarol was interrupted for periods of six days to four months. Three additional systemic embolic episodes in 2 patients occurred during the temporary Dicumarol withdrawal. One patient had a pulmonary infarction when heparin administration was interrupted. Hemorrhagic phenomena necessitating vitamin K_1 therapy appeared in 3 patients. This study indicates that long-term Dicumarol administration is effective as prophylaxis against recurrent embolism in persons with chronic rheumatic heart disease and that it is applicable to outpatients.